U.S. DEPARTMENT OF COMMERCE
National Technical Information Service

PB-246 356

INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS

HALOETHERS

SYRACUSE UNIVERSITY

PREPARED FOR
ENVIRONMENTAL PROTECTION AGENCY

SEPTEMBER 1975

318016

PB 246 356

EPA-560/2-75-006

INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS: HALOETHERS

September 1975

FINAL REPORT

Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

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INVESTIGATION OF SELECTED
POTENTIAL ENVIRONMENTAL CONTAMINANTS:
HALOETHERS

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September 1975
Final Report
Contract No. 68-01-2202
Project L1256-05

Project Officer
Frank Kover

Prepared for

Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

Document is available to the public through the National Technical Information Service, Springfield, Virginia 22151

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IBLIOGRAPHIC DATA SHEET

1. Report No. EPA 560/2-75-006

2.

3. Recipient's Accession No. PB 246 356

Title and Subtitle

Investigation of Selected Potential Environmental Contaminants: Haloethers

5. Report Date Published, September, 1975

6.

Author(s) Patrick R. Durkin, Philip H. Howard, Jitendra Saxena

8. Performing Organization Rept. No. TR-75-561

9. Performing Organization Name and Address

Life Sciences Division
Syracuse University Research Corporation
Merrill Lane, University Heights
Syracuse, New York 13210

10. Project/Task/Work Unit No.

11. Contract/Grant No. EPA 68-01-2996

2. Sponsoring Organization Name and Address

Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

13. Type of Report & Period Covered Final Technical Report

14.

15. Supplementary Notes

16. Abstracts

This report reviews the potential environmental hazard from the commercial use of haloether compounds. The fluorinated anesthetic ethers, methoxyfurane (2,2-dichloro-1,1-difluoroethyl methyl ether) and fluroxene (2,2,2-trifluoroethyl vinyl ether), are only peripherally treated. Major focus is on the α-chloroethers, bis(chloromethyl)-ether and chloromethyl methyl ether, and the β-chloroethers, bis(2-chloroisopropyl)-ether, bis(2-chloroethyl)ether, and bis(2-chloroethoxy)methane. The α-chloroethers are used as chemical intermediates for production of ion exchange resins while the β-chloroethers are used mostly for solvents but have some chemical intermediate uses. Information on physical and chemical properties, production methods and quantities, commercial uses and factors affecting environmental contamination, as well as information related to health and biological affects, are reviewed.

17. Key Words and Document Analysis. 17a. Descriptors

Haloethers
bis(chloromethyl)ether
chloromethyl methyl ether
chlorex
bis(2-chloroethyl)ether
bis(2-isopropyl)ether
toxicology
pollution
chemical marketing information

17b. Identifiers/Open-Ended Terms

Pollution
Environmental effects
Carcinogens
Solvents

17c. COSATI Field/Group

18. Availability Statement

Document is available to public through
The National Technical Information Service,
Springfield, Virginia 22151

19. Security Class (This Report) UNCLASSIFIED

20. Security Class (This Page) UNCLASSIFIED

21. No. of Pages 178

22. Price 750

FORM NTIS-35 (REV. 10-73) ENDORSED BY ANSI AND UNESCO. THIS FORM MAY BE REPRODUCED USCOMM-DC 8265-P74

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Executive Summary

Chloroethers appear to be the most important commercial haloethers. In terms of environmental hazard, the chloroethers can be divided in two categories, (1) α-chloroethers and (2) non-α-chloroethers. These two groups differ drastically in terms of uses, environmental stability and contamination, and toxicity.

Chloromethyl methyl ether (CMME), which usually contains a small amount of bis(chloromethyl)ether (BCME), is the only commercial α-chloroether. It is used as a chemical intermediate in the synthesis of strong base ion exchange resins, but the quantities used and the losses to the environment are unknown. Ion exchange resins have important applications in water conditioning and as a method of separation for chemical processes. The two compounds are very reactive and have extremely short half-lives in water (< 1 second for CMME and < 1 minute for BCME), although they are more stable in the vapor phase ($t_{\frac{1}{2}}$ > 390 minutes for CMME and > 25 hours for BCME). Normally, compounds that are used as chemical intermediates and are relatively non-persistent would have little environmental significance. However, BCME has been demonstrated to be one of the most carcinogenic compounds known (6 hour inhalation exposure to 0.1 ppm induces respiratory tract cancer in rats). Industrial exposure to the CMME-BCME combination has led to at least 47 human deaths from respiratory cancer. Because of the extreme toxicity, it would seem worthwhile to determine if sizable quantities of CMME and BCME are being released to the environment, especially the atmosphere. However, due to the high reactivity of α-chloroethers, they would appear to be more of an occupational, rather than an environmental problem.

In contrast, β-chloroethers are widespread environmental contaminants. Contamination of raw and drinking water by bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether is well documented by monitoring, and the β-chloroethers are considerably more chemically stable than the α-chloroethers. However, the sources of contamination are not well understood [although the propylene chlorohydrin process for producing propylene oxide (capacity - 900 million pounds a year) is implicated], nor is the available production and use information very exact. These two β-chloroethers are less corrosive than the α-chloroethers [fatal inhalation concentration above 100 ppm for bis(2-chloroethyl)ether] and have not been as intensively screened for carcinogenicity. Nevertheless, one study has demonstrated the apparent oral carcinogenicity of bis(2-chloroethyl)ether. By other routes of administration, β-chloroethers show no marked carcinogenic activity. Since the β-chloroethers are (1) produced or may be formed as by-products in sizable quantities, (2) are released to and appear to persist in the environment, (3) can pass through drinking water treatment plants, and (4) may be carcinogenic, it is suggested that intensive research and study of these compounds be undertaken.

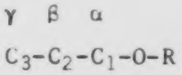
Investigation of Selected Potential Environmental Contaminants: Haloethers

I. Physical and Chemical Data

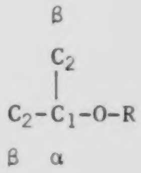
A. Structure and Properties

1. Chemical Structure

Haloethers are compounds which contain an ether moiety (R-O-R) and a halogen atom attached to the alkyl or aryl substituent. When the compound is named as an ether, the numbering or lettering of the carbons begins at the carbon next to the oxygen. Thus, for example, an α-haloalkyl (or 1-halo) ether has at least one halogen attached to the carbon next to the oxygen.



$\overset{\gamma}{C_3}-\overset{\beta}{C_2}-\overset{\alpha}{C_1}-O-R$



$\underset{\beta}{C_2}-\underset{\alpha}{\overset{\overset{\beta}{C_2}}{\overset{|}{C_1}}}-O-R$

This review has considered only ethers which have a halogen substituted on an alkyl chain; aryl halogen substituted ethers were excluded. The review focuses upon compounds that appeared to have commercial or environmental significance. The compounds which received the most attention during the literature search are listed in Table 1. These compounds were chosen because they appeared either in the U.S. Tariff Commission (1972) reports of commercial synthetic organic chemicals, the Directory of Chemical Producers (S.R.I., 1974), or the Kirk-Othmer Encyclopedia of Chemical Technology (Lurie, 1965; Krantz, 1963). A considerable amount of information on bis(chloromethyl)ether and chloromethyl methyl ether has been reviewed in this report; for brevity, these compounds have been assigned the acronyms BCME and CMME, respectively.

2. Physical Properties

Non-halogenated ethers are pleasant smelling, colorless liquids with densities of less than 1.0. They are neutral, volatile,

Table 1. **Physical Properties of Haloethers (Lurie, 1965; Allen, 1956; Tschamler, 1950; Krantz, 1963; Hake and Rowe, 1963)**

Ether	Structure	Boiling Point (°C)	Melting Point (°C)	d_{20}	n_D^{20}	Vapor Pressure (mm Hg)	Solubility in water (g/100 ml)	Specific Heat (cal/mole)	Surface Tension	Dipole Moment ($\mu \times 10^{18}$)	Dielectric Constant	Viscosity (cP)
bis(chloromethyl)	$(C\ell CH_2)_2O$	105	-103.5	1.315	1.4421							
bis(2-chloroethyl) (Chlorex)	$(C\ell CH_2CH_2)_2O$	178	- 46.7	1.2199	1.4572	0.73	1.07	0.369	42		21	2.372
bis(2-chloroisopropyl)	$(C\ell CH_2\overset{\overset{CH_3}{\vert}}{C}H)_2O$	187	- 99	1.1127	1.4505	0.71-0.85	0.17					
bis(2-chloroethoxy) methane	$(C\ell CH_2CH_2O)_2CH_2$	105-106		1.225	1.4557							
chloromethyl methyl	$C\ell CH_2OCH_3$	61		1.3974	1.0605					2.03		
2-(2-chloroethoxy)ethyl 2-chloroethyl	$C\ell CH_2CH_2OCH_2CH_2OCH_2CH_2C\ell$											
dichloromethyl methyl	$C\ell_2CHOCH_3$	84.5		1.270	1.4299							
dichloromethyl chloromethyl	$C\ell_2CHOCH_2C\ell$	129		1.464	1.4622							
bis(dichloromethyl)	$C\ell_2CHOCHC\ell_2$	143		1.558	1.4728							
trichloromethyl methyl	$C\ell_3COCH_3$	106-110		1.4391	1.4536							
trichloromethyl dichloromethyl	$C\ell_3COCHC\ell_2$	159										
1-chloroethyl ethyl	$CH_3CHC\ell OC_2H_5$	28_{57}		0.9495	1.4021							
2-chloroethyl ethyl	$C\ell CH_2CH_2OC_2H_5$	106		0.9945	1.412							
bis(1-chloroethyl)	$(CH_3CHC\ell)_2O$	113		1.106	1.4186							
bis(2-bromoethyl)	$(BrCH_2CH_2)_2O$	115_{32}		1.8227	1.5131							
bis(2-chloropropyl)	$(CH_3CHC\ell CH_2)_2O$	188		1.109	1.4467							
bis(3-chloropropyl)	$(C\ell CH_2CH_2CH_2)_2O$	215		1.4120								
bis(4-chlorobutyl)	$(C\ell CH_2CH_2CH_2CH_2)_2O$	$84\text{-}86_{5.5}$		1.0691	1.4562							
2-chloroethyl vinyl	$C\ell CH_2CH_2OCH{=}CH_2$	109	-70	1.0493	1.4381		0.6					
chloromethyl ethyl	$C\ell CH_2OCH_2CH_3$	84			1.4040							
chloromethyl phenyl	$C\ell CH_2OC_6H_5$	$88\text{-}90_{15}$	- 3									
2,2-dichloro-1,1-difluoroethyl methyl (methoxyfurane)	$CHC\ell_2CF_2OCH_3$	104										
2,2,2-trifluoroethyl vinyl (Fluroxene or Fluoromar)	$CF_3CH_2OCH{=}CH_2$	43.2		1.13		286	0.4					

flammable compounds, which have little or no solubility in water but are miscible with most organic liquids (Lurie, 1965).

The majority of the compounds listed in Table 1 are chloroethers. Chlorine substitution on ethers has a tendency to increase the density, boiling point, and odor, decrease the flammability, and alter the solubility properties. For example, diethyl ether has a density of 0.714 and boiling point of 34.5°C, a pleasant odor, and is very flammable (flash point, closed-cup; -49°C). In contrast, bis(2-chloroethyl)ether has a density of 1.219 and boiling point of 178°C, a pungent odor, and is much less flammable (flash point, open cup; 84°C). The fluorine substituted compounds (last two compounds in Table 1), which find commercial applications as anesthetics, are much more volatile than their chlorinated analogues. Other general physical properties for the haloethers are listed in Table 1.

Some of the commercial applications of the haloethers are dependent upon the solubility of the compounds. For example, bis(2-chloroethyl)ether has been used to separate lubricating stocks into paraffinic and naphthenic fractions. A comparison of the solubility of bis(2-chloroethyl)ether with two other solvents is presented in Table 2.

3. Principal Contaminants in Commercial Products

Of the haloethers that have been reviewed, only six, including the two anesthetics, appear to be produced in commercial quantities (see Section II-A, p.25). The two anesthetics, methoxyfurane ($CHC\ell_2CF_2OCH_3$) and fluroxene ($CF_3CH_2OCH{=}CH_2$), are probably highly purified before use since they are meant for human consumption. However, information

Table 2. Solubility of Fats, Oils, Waxes, Resins, Balsams, and Dyes in Commercial Isopropyl Ether, Dichloroethyl Ether, and Ethylene Dichloride (Fife and Reid, 1930)

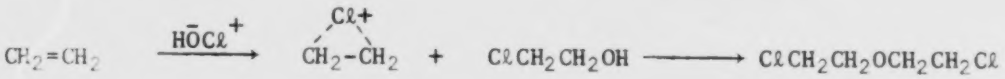
Solute	Iso-Propyl Ether	Dichloro-Ethyl Ether	Ethylene Dichloride
Crisco	S	S	S
Vaseline	S	SH	SH
Mazola	S	S	S
Wesson oil	S	S	S
Mineral oil	S	SH	S
Citronella	S	S	S
Juniper	S	S	S
Coriander	S	S	S
Sweet birch	S	S	S
Menthol	S	S	S
Castor oil	S	S	S
Linseed oil	S	S	S
Cottonseed oil	S	S	S
Venetian turpentine	S	S	S
Japan wax	S	SH	S
Carnauba wax	SS	SH	PSH
Beeswax	SH	SH	SH
Paraffin wax	S	S	S
Amberol	S	S	S
Albertol	S	S	S
Aroclar 1254	S	S	S
Rezyl balsam	S	S	S
Rezyl resins	S	S	PS
Varnish-type glyptals	S	S	S
Sarpee	SS	PSH	SSH
East India	PSH	PSH	PSH
Bakelite R. 352	S	S	S
Gum-Lac	S	SH	S
Coumarone	SH	S	S
Cumar	S	S	S
Manilla	SSH	SSH	S
Ester gum	S	S	S
Ester gum (oxidized)	S	S	S
Rosin	S	SH	S
Abietic acid (purified)	S	SH	SH
Beckacite	PSH	PSH	S
G. P. O. Resin	S	S	S
Ester gum (acetylated)	S	S	S
G.E. Resin (Bakelite type)	S	S	S
Manta gum	S	SSH	SSH
Dammar	SH	SH	S
Congo	S	PSH	PSH
Kauri	SH	SH	PSH
Zopal	S	S	S
Zinc resinate	S	S	S
Laculose (A)	PSH	SH	PSH
Gilsonite	I	S	S
Sandarac	SSH	PSH	SSH
Montol resin	S	S	S
Pontianac	I	SH	PSH
Gum mastic	I	S	S
Benzyl abietate	S	S	S
Shellac	SSH	PSH	SSH
Vinylite 80	I	PSH	S
Vinylite A	I	I	S
Casein (rennet)	SSH	SSH	SSH
Nitrocellulose	I	SS	I
Cellulose acetate	I	SH	I
Benzyl cellulose	I	SH	S
Ethyl cellulose	S	S	S
Camphor	S	S	S
Spirit-soluble yellow	S	PSH	PSH
Spirit-soluble red	S	PSH	PSH
Spirit-soluble nigrosene	I	S	S
Water-soluble nigrosene	S	I	I
Oil-soluble nigrosene	S	S	S
Oil-soluble blue	S	SH	SH
Oil-soluble yellow	S	S	S
Oil-soluble black	S	S	S
Indigosol	I	PSH	I
Spirit-soluble black	I	SH	SH
Spirit-soluble blue	PS	S	S
Oil-soluble green	I	PS	I
Indigo	S	S	S
Benzo brown 36A	PSH	PSH	PSH
Alizarine sky blue	SS	S	S
Victoria blue B	SS	S	S
Diazo brown Scarlet S B A	SSH	PSH	PSH

S = Soluble at room temperature
SS = Slightly soluble at room temperature
SH = Soluble hot
PS = Partially soluble
PSH = Partially soluble hot
I = Insoluble

on the analysis of the commercial products for trace contaminants is not available. With fluroxene, a non-volatile stabilizer is added (0.01% of N-phenyl-1-naphthylamine) to prevent polymerization and hydrolysis (Ohio Medical Products, 1972).

As with the anesthetics, the other commercial haloethers -- bis(chloromethyl), chloromethyl methyl, bis(2-chloroethyl), and bis(2-chloroisopropyl) ethers -- have not been extensively analyzed for trace contaminants. In fact, in many instances these compounds may be trace contaminants in other commercial products (e.g. bis(2-chloroethyl) and bis(2-chloroisopropyl) ethers in ethylene and propylene chlorohydrins) (see Section II-C-7, p.63). However, Collier (1972) has reported that bis(chloromethyl)ether (BCME) is typically found as several percent (1 to 7%, Figueroa et al., 1973) of commercial chloromethyl methyl ether (CMME), which is made by reacting gaseous HCℓ with a heated solution of formaldehyde and methanol.

The other commercial chloroethers are also not produced by direct chlorination and, therefore, probably have little chloroether by-products. For example, bis(2-chloroethyl)ether is formed during the synthesis of ethylene chlorohydrin.

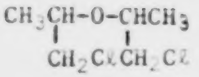
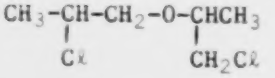
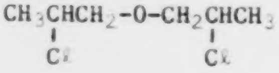


$$CH_2{=}CH_2 \xrightarrow{H\bar{O}Cl^{+}} \overset{Cl^{+}}{CH_2{-}CH_2} + ClCH_2CH_2OH \longrightarrow ClCH_2CH_2OCH_2CH_2Cl$$

However, with propylene chlorohydrin two chlorohydrins are possible which result in three possible ethers (see Figure 9, p. 36). Two isomer ratios have been reported, suggesting that the quantities of chloroether isomers noted in Table 3 would be found in the commercial product.

Table 3. Isomers of Chloroisopropyl Ethers

Found as By-Products of Propylene Chlorohydrin

	Ratio of Attack at Secondary vs. Primary Carbon	
	3:1	9:1
 $CH_3CH(CH_2Cl)-O-CH(CH_2Cl)CH_3$	56%	81%
 $CH_3-CH(Cl)-CH_2-O-CH(CH_2Cl)CH_3$	38%	18%
 $CH_3CH(Cl)CH_2-O-CH_2CH(Cl)CH_3$	6%	1%

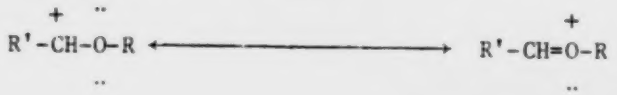
When bis(2-chloroethyl)ether is heated during use as an extraction solvent, traces of hydrochloric acid are formed resulting in a corrosion problem. In order to reduce this problem, inhibitors are added to the solvent. Pollard and Lawson (1955) have evaluated a number of inhibitors, such as ammonia, diethyl aminoethanol, tri-cresyl phosphate, tertiary heptyl mercaptan, and two commercial amine-type inhibitors, for use with bis(2-chloroethyl)ether and, therefore, these additives might be found in commercial formulations.

B. Chemistry

1. Reactions Involved in Uses

There is considerable difference between the reactivity of α-haloalkyl ethers and ethers in which the halogen is substituted on a carbon that is not attached to the ether oxygen. The high reactivity of the α-haloethers is a result of the two electronegative atoms, oxygen and halogen, which are bonded to the same carbon (Summers, 1955). This difference in reactivity is particularly evident in the different rates of hydrolysis (see Section I-B-2, p. 11).

The major application of CMME, the only α-haloether that is used in substantial commercial quantities, is as a chloromethylating agent in the production of anion exchange resins. The compound is used as the swelling solvent as well as the reactant, and the reaction takes place under Fiedel-Crafts conditions (see Figure 1a). Chloromethylation using α-haloethers is somewhat unusual because most displacement reactions of α-haloethers, whether under basic or acidic conditions, result in products in which the halogen rather than the oxygen is displaced (Summers, 1955). This reactivity of the chlorine atom has been attributed to the possibility for resonance stabilization.



$$R'-\overset{+}{C}H-\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}-R \longleftrightarrow R'-CH=\underset{\cdot\cdot}{\overset{+}{O}}-R$$

Under proper Fiedel-Crafts conditions, both the chloromethyl derivative and the benzyl ether can be formed (Figure 1b,c). However, the chloromethylation product always predominates, and the benzyl ether yields are always very low (Summers, 1955). In contrast, α-haloethers under Fiedel-Crafts conditions add across the double bond of olefins (Figure 1d).

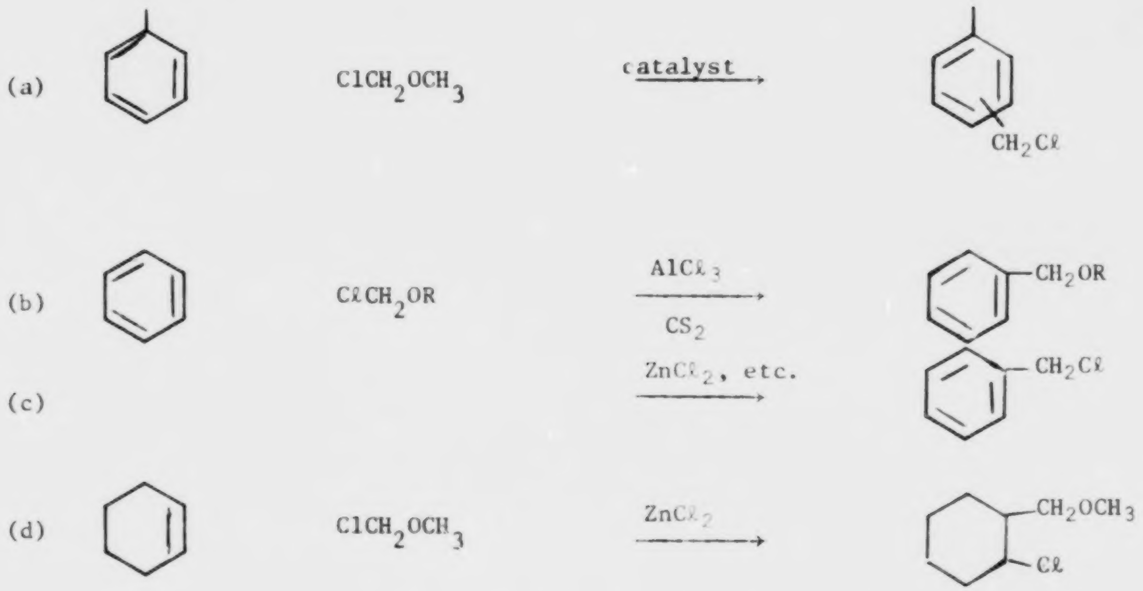


Figure 1. Chloromethylation with Chloromethyl Methyl Ether (Wheaton and Seamster, 1966; Summers, 1955)

The other principal chemical intermediate application of haloethers is the manufacture of polysulfides from bis(2-chloroethoxy)methane (Berenbaum and Johnson, 1968). Figure 2 illustrates the chemical reaction involved in the polymerization process.

$$C\ell CH_2CH_2OCH_2OCH_2CH_2C\ell + H_2S_x \longrightarrow \left[S{-}SCH_2CH_2OCH_2OCH_2CH_2\right]_x$$

Figure 2. Formation of Polysulfides

Other minor chemical intermediate applications have been noted in the available literature. Some of these are summarized in Figure 3 (see Table 21, p. 50, for a full list of minor chemical intermediate uses).

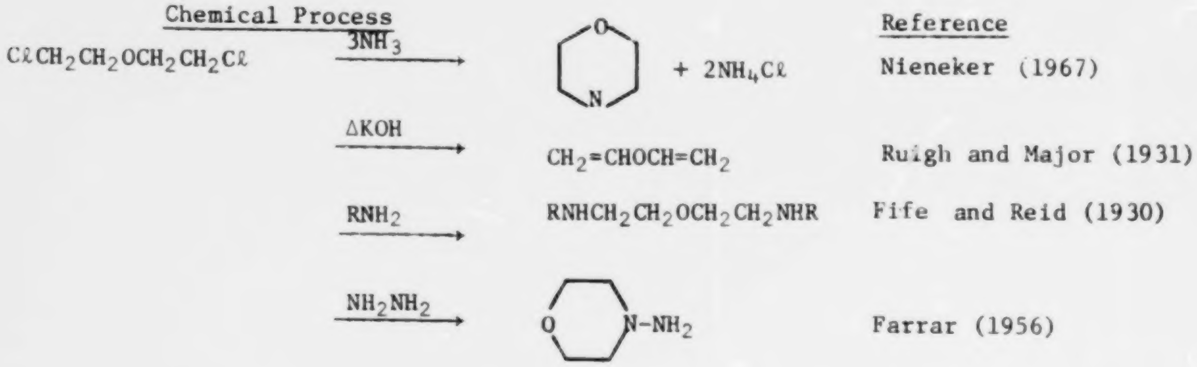


Figure 3. Minor Chemical Intermediate Applications of Haloethers

2. Hydrolysis

As noted above, there is a considerable difference between the reactivity of α-haloethers and ethers with halogens on carbon atoms not connected to the ether function. However, this difference cannot be demonstrated with the two commercial fluorinated haloethers, mostly because of a lack of information. No information was obtained on the hydrolytic stability of methoxyflurane ($CHCℓ_2$-CF_2OCH_3). Since two fluorine atoms are substituted in the α-position, it might be suspected that the compound would hydrolyze rapidly. However, because fluorine is a poor leaving group and the C-F bond is extremely strong (C-F = ~ 116 Kcal/mole compared to C-H = 99 Kcal/mole), hydrolysis of methoxyflurane is probably quite slow. The other commercial fluoroether, fluroxene (CF_3CH_2-$OCH=CH_2$), does not contain an α-halogen. It does not hydrolyze in solutions buffered between pH 2.0-11.0 when incubated for 3 hrs at 38°C (Ohio Medical Products, 1972). Because of its stability, fluroxene can be used in a closed circuit anesthesia system with carbon dioxide absorption with a 70-100°C soda lime solution. However, the commercial product usually contains a stabilizer to prevent polymerization and hydrolysis, which may take place in the presence of moisture and air.

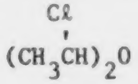
$$CF_3CH_2OCH{=}CH_2 \longrightarrow CF_3CH_2OH + CH_3\overset{O}{\overset{\|}{C}}H$$

Salomaa and coworkers (1966) have also indicated that under acidic conditions vinyl ethers are readily hydrolyzed to an aldehyde and alcohol.

$$C\ell CH_2CH_2OCH{=}CH_2 \xrightarrow[25°C]{H_3O^+} C\ell CH_2CH_2OH + CH_3\overset{O}{\overset{\|}{C}}H (K = 0.168M^{-1}sec^{-1})$$

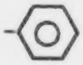
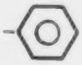
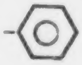
For the chloroethers, the contrast between hydrolysis reactivity for α-chloroethers compared to other chloroethers is best demonstrated in the work of VanDuuren and coworkers (1972). These researchers investigated the kinetics of hydrolysis by placing known quantities (10-50 μl) of the chloroethers in a 10 ml solution of water-dimethylformamide (3:1). By titrating the hydrochloric acid formed with an automatic recording titrator (pH maintained at 7.0), the pseudo first-order rate constants were calculated. The results are tabulated in Table 4. All compounds containing an α-chloro substituent have a half life of less than 2 minutes; compounds with no chlorine atom in the α-position have half-lives greater than one day.

Table 4. Rate of Hydrolysis of Chloroethers in H_2O-DMF (3:1) (Van Duuren et al., 1972)

Chemical	Formula	Temperature (°C)	Rate (min^{-1})	$t_{\frac{1}{2}}$ (min)
Bis(1-chloroethyl) ether	 $(CH_3\overset{Cl}{C}H)_2O$	0	$>3.5 \times 10^{-1}$	<2
Chloromethyl methyl ether	$ClCH_2OCH_3$	0	$>3.5 \times 10^{-1}$	<2
Bis(chloromethyl) ether	$ClCH_2OCH_2Cl$	0	$>3.5 \times 10^{-1}$	<2
1,1-Dichloromethyl methyl ether	Cl_2CHOCH_3	0	$>3.5 \times 10^{-1}$	<2
Bis(2-chloroethyl) ether	$(ClCH_2CH_2)_2O$	30	$<5.0 \times 10^{-4}$	>23 hr
Octachloro-di-n-propyl ether		30	$<5.0 \times 10^{-4}$	>23 hr

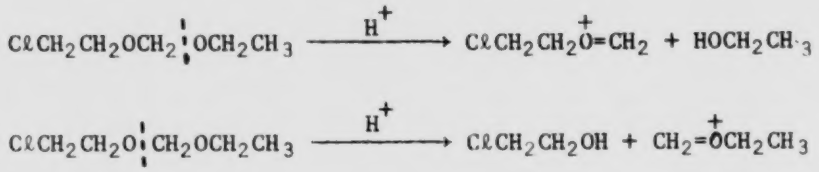
The rates of hydrolysis of the non-α-chloroethers are very similar to the hydrolysis rate of simple alkyl halides. This is illustrated by the work of Böhme and Sell (1948), who studied the hydrolysis of β, γ, and δ-chloroethers and chlorothioethers and several alkyl chlorides in a dioxane-water mixture (20 M water in dioxane). The kinetics were run at a temperature of 100°C. Table 5 presents the measured hydrolysis rates of reaction and half-lifes for the chloroethers and alkyl chlorides. The only compound studied by both Van Duuren et al. (1972) and Böhme and Sell (1948) is bis(2-chloroethyl)ether. Considering that the studies were done in different solvents and at different temperatures, the rates obtained seem to be reasonable ($t_{\frac{1}{2}}$ = > 24 hr compared to 12.8 days).

Table 5. Hydrolysis of β-, γ-, δ-Chloroethers in 20 M Water in Dioxane Solution at 100°C (Böhme and Sell, 1948)

Compound	K (min^{-1})	$t_{\frac{1}{2}}$ (days)
$C\ell CH_2CH_2OCH_2CH_3$	0.000011	17.5
$C\ell CH_2CH_2O$ - 	0.0000056	34.3
$(C\ell CH_2CH_2)_2O$	0.000015	12.8
$C\ell CH_2CH_2CH_2OCH_2CH_3$	0.000048	4.0
$C\ell CH_2CH_2CH_2O$ - 	0.000023	8.3
$C\ell CH_2CH_2CH_2CH_2O$ - 	0.000052	3.7
$CH_3CH_2CH_2CH_2C\ell$	0.000062	3.1
$C\ell CH_2CH_2CH_2CH_2C\ell$	0.000089	2.1
$CH_3CH_2CH_2CH_2CH_2CH_2C\ell$	0.000053	3.6

Interestingly enough, the thioether analogue of bis(2-chloroethyl)ether, commonly referred to as mustard gas, hydrolyses approximately 4000 times as fast as the ether.

As noted earlier, Salomaa et al. (1966) have studied the hydrolysis of vinyl ethers under acid conditions. These authors have also demonstrated that chlorine substituted acetals are readily hydrolyzed under acid conditions (see Figure 4).



$$C\ell CH_2CH_2OCH_2 \vdots OCH_2CH_3 \xrightarrow{H^+} C\ell CH_2CH_2\overset{+}{O}{=}CH_2 + HOCH_2CH_3$$

$$C\ell CH_2CH_2O \vdots CH_2OCH_2CH_3 \xrightarrow{H^+} C\ell CH_2CH_2OH + CH_2{=}\overset{+}{O}CH_2CH_3$$

Figure 4. Hydrolysis of Chloroacetals (Salomaa *et al.*, 1966)

The instability of α-haloethers under hydrolysis conditions has been recognized for some time. For example, in 1941, Bohme (see Summers, 1955) showed that the hydrolysis rate constant for 1-chloroethyl ethyl ether was only approximately 20 times less than the rate constant for acetyl chloride (very violent reaction with water). Bohme and Dorries (1956) examined the hydrolysis and alcoholysis rates of a variety of chloromethyl ethers in dioxane. The results are summarized in Table 6. These results demonstrate that with aryl chloromethyl ethers hydrolysis is very slow. In fact, chloromethyl phenyl ether may be washed with water or aqueous sodium biocarbonate during preparation (Summers, 1955).

Table 6. Solvolysis of Chloromethyl Ethers in Dioxane (Bohme and Dorries, 1956)

				$k(min^{-1})$			
		Water					Methanol
Compound	1%	2%	3%	5%	10%	20%	5%
$C\ell CH_2OC_6H_5$		0.000035		0.00041	0.0019	0.012	0.000019
$C\ell CH_2OCH_2C_6H_5$		0.015	0.046				0.0060
$C\ell CH_2OCH_3$		0.038					0.0073
$C\ell CH_2OCH_2CH_3$	0.013	0.14					0.022

The more recent studies on haloether hydrolysis have concentrated on determining the stability of CMME and BCME in water (and other solvolysis media) and in humid atmospheres. The studies of the rates of hydrolysis in these two environments will be discussed separately.

Ribar and Glavas (1968) studied the rate of hydrolysis of CMME in 95% aqueous acetone at 0°C in an attempt to clarify the mechanism of reaction. They concluded that the reaction was not autocatalyzed by the hydrogen chloride that is generated by hydrolysis, as had previously been reported, and that the reaction may proceed by either an S_N1 or S_N2 mechanism (see Figure 5). The experimental results are presented in Table 7.

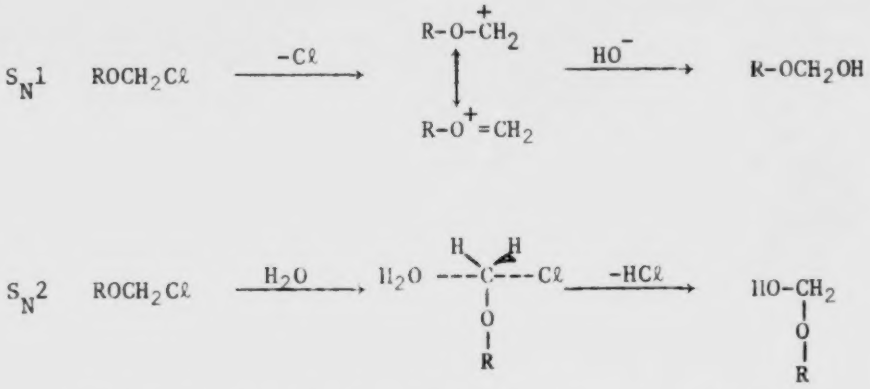


Figure 5. S_N1 and S_N2 Mechanisms for the Hydrolysis of Chloromethyl Ethers

Table 7. Hydrolysis Rate Constants for Chloromethyl Methyl Ether in 95% Aqueous Acetone at 0.0°C (Ribar and Glavas, 1968)

Added salt (mol/liter)	$K \times 10^4$ (sec^{-1})	$t_{\frac{1}{2}}$ (min)
-	5.38 ± 0.10	21
2.50×10^{-3} LiCℓ	9.82 ± 0.13	11
5.00×10^{2} $LiNO_2$	7.58 ± 0.09	15
4.0×10^{-3} HCℓ	6.68 ± 0.21	17
5.40×10^{-2} HCℓ	7.82 ± 0.16	15
-	1.45 ± 0.30 (-20°C)	80

Jones and Thornton (1967) also studied the solvolysis mechanism of CMME. They concluded that "the solvolysis of methyl chloromethyl ether is S_N1 like, resembling t-butyl chloride in spite of the steric possibility of a tight, S_N2-like transition state." Some of the reported solvolysis rates are listed in Table 8.

Tou and coworkers (Tou and Kallos, 1974a, Tou, et al., 1974) have examined the hydrolysis rates of BCME in aqueous systems. During a study of the possible formation of BCME in aqueous HCℓ and HCHO mixtures, Tou and Kallos (1974a) determined the rate of hydrolysis of BCME at ambient

Table 8. Solvolysis Rates of Chloromethyl Methyl Ether (Jones and Thornton, 1967)

Solvent	Temperature (°C)	$K \times 10^2$ (sec^{-1})	$t_{\frac{1}{2}}$ (sec)
2-propanol	24.87	4.791	14
2-propanol	0.0	0.738	94
2-propanol	15.1	2.486	28
95.2% acetone H_2O	24.87	0.4198	165
95% dioxane H_2O	24.87	0.3402	203
90% dioxane H_2O	24.87	3.507	20
ethanol	24.87	13.305	5.2
methanol	24.87	135 (extrapolated)	0.5

temperature in five acidic solutions [(1) 1 ppm HCℓ and 1 ppm HCHO, (2) 10 ppm HCℓ and 10 ppm HCHO, (3) 100 ppm HCℓ and 100 ppm HCHO, (4) 250 ppm HCℓ and 250 ppm HCHO, (5) 1000 ppm HCℓ and 1000 ppm HCHO] and in deionized water. The hydrolysis rate constant was $k = 0.050\ sec^{-1}$ ($t_{\frac{1}{2}}$=14 sec) in all cases, and was independent of the HCℓ and formaldehyde concentrations. In a more intensive study of BCME hydrolysis rates and mechanism of reaction, Tou et al. (1974) studied the hydrolysis of BCME under both acidic and basic conditions. Their reaction vessel is depicted in Figure 15 (see p. 71). The rates of hydrolysis measured at 1 ppm of BCME are presented in Table 9.

Table 9. Hydrolysis of Bis(chloromethyl)ether in Water and Aqueous HCℓ and NaOH (Tou *et al.*, 1974)

	0°C		20°C		40°C	
Solution	R(sec^{-1})	$t_{\frac{1}{2}}$ (sec)	R(sec^{-1})	$t_{\frac{1}{2}}$ (sec)	R(sec^{-1})	$t_{\frac{1}{2}}$ (sec)
2N NaOH	0.0079	88	0.024	29	0.064	11
1N NaOH	0.0064	108	0.032	22	0.13	5
H_2O	0.0025	277	0.018	38	0.10	7
1N HCℓ	0.0019	365	0.018	38	0.12	6
3N HCℓ	0.0011	630	0.011	63	0.088	8

From the measured energy of activation and entropy of activation, these researchers concluded that the hydrolysis of BCME "is S_N1 in character in basic solutions and shifts to an S_N2-like mechanism in acidic solutions." It was postulated that carbonium ion stabilization by charge delocalization ($[ClCH_2OCH_2^+]Cl^- \longleftarrow [ClCH_2\overset{+}{O}=CH_2]Cl^-$) is not possible under acidic conditions because of the protonation of the ether oxygen atom.

The hydrolysis of CMME in water has not been measured because of its high reactivity. Tou and Kallos (1974b) have estimated that the half-life is less than 1 second based on extrapolations of the solvolysis study of Jones and Thorton (1967). Nichols and Merritt (1973) demonstrated that the solvolysis rate of CMME is orders of magnitude greater than BCME.

In aqueous methanol at 45°C, they found a rate ratio of ≃1:5,000, and they estimated a rate ratio of CMME:BCME at 0°C in 25% DMF - 75% H_2O (solvent system used by VanDuuren *et al.*, 1972) to be approximately 1:1.5 x 10^6. With these relative rates in mind and the hydrolysis data of Tou *et al.* (1974) for BCME, a half-life of less than 1 second seems reasonable for CMME.

This difference between the reactivity of BCME and CMME is also noticeable in vapor phase studies. Collier (in Nichols and Merritt, 1973) determined the reactivity of the two compounds in 70% relative humidity at 25°C. These results are presented in Table 10. Frankel *et al.* (1974) also noted the stability of BCME in recovery studies of 1, 5, and 12 ppb BCME in Saran bags maintained for 18 hr at 26°C and 40% relative humidity.

Table 10. Vapor Phase Reactivity (25°C)
(L. Collier as reported in Nichols and
Merritt, 1973)

Concentration	Relative Humidity* (percent)	$t_{\frac{1}{2}}$ (min)
100 ppm CMME	70	6
1000 ppm CMME	70	3.5
10 ppm BCME	70	No reaction after 18 hours
100 ppm BCME	70	"

* 1 mole CMME/100 moles H_2O

In a much more detailed study, Tou and Kallos (1974b) examined the vapor phase reactivity of BCME and CMME using different water concentrations and reactor material. Their results are presented in Table 11.

The results of Tou and Kallos (1974b) strongly suggest a surface catalyzed reaction for CMME, thus suggesting that both BCME and CMME may persist in the atmosphere for extended periods of time. These researchers concluded that "stability data on CMME cannot be extrapolated from a glass system to atmospheric environment" and that even the results that were obtained with the Saran reactor material should only be considered as the upper limits of the rate of hydrolysis. Therefore, the upper limits of the rate of hydrolysis taking place in the gas phase were 0.0018 min^{-1} (or $t_{\frac{1}{2}}$>390 min) and 0.00047 min^{-1} (or $t_{\frac{1}{2}}$>25 hr) for CMME and BCME, respectively, under the temperature and water concentration conditions used.

3. Oxidation and Photochemistry

No studies have been located concerning the oxidative or photolytic reactivity of the haloethers of interest to this report. However, ethers in general are very stable compounds. Upon prolonged exposure to air, some ethers will autooxidize to peroxides (Lurie, 1965). This does not appear to occur with trifluoroethyl vinyl ether (Ohio Medical Products, 1972). Strong oxidizing conditions tend to cleave unsubstituted ethers to yield the corresponding aldehyde and carboxylic acid (Lurie, 1965). Whether haloethers react in a similar way is unknown.

Table 11. Surface Effect on the Gaseous Hydrolysis Rates of Chloromethyl Methyl Ether (A) and Bis(chloromethyl)-ether (B) Near Ambient Temperature (Tou and Kallos, 1974b)

Compounds	Reactor Material	Temperature (°C)	Water concentration (% by volume)	Relative humidity (%)	$k(min^{-1})$	$t_{\frac{1}{2}}$ (min)
A	Glass	25	1.7	53	0.028	25
		25	2.2	69	0.12	5.8
	Fused ground glass	26	1.6	47	0.12	5.8
	Teflon	27	1.5	42	0.0059	120
		25	1.9	60	0.014	50
		25	2.1	65	0.035	20
	Saran	29	1.6	39	0.0018	390
		25	2.0	62	0.0058	120
		29	2.2	54	0.0060	120
	Fe_2O_3 powder-coated Saran	25	1.1	35	0.042	17
		25	2.3	72	0.31	2.3
B	Glass	25	2.2	67	0.00057	1200 (20 hr)
	Fused ground glass	25	2.6	81	0.0047	1500 (25 hr)
	Fe_2O_3 powder-coated Saran	23	1.2	42	0.0013	540 (9.0 hr)
		23	2.3	81	0.0016	430 (7.2 hr)

Alkyl ethers, even halogenated ones, are not strong absorbers of ultraviolet light, and, therefore, if they are to react photochemically, they must derive energy from light indirectly (e.g., sensitization). No studies are available on the photolysis of the alkyl haloethers being reviewed in this report. However, a study by Stenberg et al. (1967) provides some insight into possible photochemical reactions. These researchers photolyzed an oxygen-saturated ethyl ether solution with Vycor filtered (>218 nm) and Pyrex filtered (>278 nm) light. The oxygen-saturated solution had a wavelength maximum at longer wavelength ($\lambda_{max} \approx 210$ nm) than a nitrogen-saturated solution, which was attributed to a charge-transfer complex. The mechanism and product formed from photolysis with the Vycor filter is depicted in Figure 6. No reaction took place when the Pyrex filter was used.

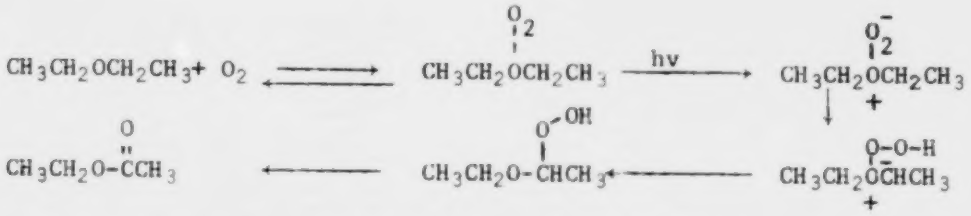


Figure 6. Photolysis Mechanism of An Oxygen-Saturated Solution of Ethyl Ether (Stenberg et al., 1967)

4. Other

The chemical difference between α-haloethers and non-α-haloethers is also apparent in the difference in thermal stability. When α-haloalkyl ethers are capable of undergoing dehydrohalogenation, the compounds readily decompose with evolution of hydrogen halide. However, the chloromethyl ethers, since they cannot undergo dehydrohalogenation, are relatively stable compounds, given the exclusion of water (Summers, 1955). Nevertheless, the chloromethyl ethers will decompose at elevated temperatures to yield the aldehyde and an alkyl chloride.

The β-chloroethers will also decompose at elevated temperatures. For example, Pollard and Lawson (1955) found that when solutions of bis(2-chloroethyl)ether and oil are heated, hydrochloric acid is formed. Barton *et al*. (1951) compared the thermal decomposition of *n*-propyl chloride and bis(2-chloroethyl)-ether. Bis(chloroethyl)ether decomposed at a slightly lower temperature (373-429°C) than *n*-propyl chloride (420-478°C) and yielded a complex mixture including divinyl ether.

Chlorination of ethers initially takes place at the α-carbon. For example, direct chlorination of ethyl ether yields 1-chloroethyl ethyl ether and then 1,2-dichloroethyl ethyl ether.

$$CH_3CH_2OCH_2CH_3 \xrightarrow{C\ell_2} CH_3CHC\ell OCH_2CH_3 \xrightarrow{C\ell_2} C\ell CH_2CHC\ell OCH_2CH_3$$

Both CMME and BCME can be produced in this manner under photochemical conditions (Summers, 1957).

For other chemical properties of haloethers see the review by Summers (1955) (α-haloalkyl ethers only) and the review of ethers in general by Lurie (1965).

II. Environmental Exposure Factors

A. Production and Consumption

1. Quantity Produced

Very little information is available on the quantities of haloethers that are produced. Of the ten compounds that have appeared in the U.S. Tariff Commission reports over the years 1959-1972 (criteria require that the chemical be produced in a quantity of 1000 lbs or have a value of $1000), only production and sales figures for bis(2-chloroethyl)ether during the late 1950's and early 1960's have been published. These quantities are depicted in Table 12. However, since bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether are produced as by-products in the chlorohydrin synthesis of ethylene and propylene oxide, respectively (see Section II-A-3, p. 30), estimates of the quantities of the two compounds produced can be determined. These estimates are also depicted in Table 12 with the references to the factors and data used in the calculations. Comparison of the 1959 and 1960 published production and the calculated production for bis(2-chloroethyl)ether indicates that the calculations provide only an order of magnitude reliability. The factor reported by Horsley (1968) (100 lbs oxide = 2 lbs ether) seems to be quite different than the effluent monitoring data of Kleopfer and Fairless (1972), thus suggesting that only a protion of the by-product that is produced is released from production facilities. The latter authors reported that approximately 150 lbs/day of bis(2-chloroisopropyl)ether was being discharged by a glycol plant 150 river miles upstream from Evansville, Ind. (probably the Olin

Table 12. Production of Haloethers (10^6 lbs)

	bis(2-chloroethyl)ether				bis(2-chloroisopropyl)ether		
	U.S. Tariff Commission		By-product of ethylene chlorohydrin		By-product of propylene chlorohydrin		
Year	Production	Sales	Ethylene oxide by chlorohydrin synthesis (Blackford, 1973a)	Ether produced (100 lbs oxide = 7-9 lbs ether) (Schultze, 1965)	Propylene oxide production (U.S.Tariff Comm.)	Production oxide by chlorohydrin synthesis (Blackford, 1973b)	Ether produced (100 lbs oxide = 2 lbs ether) (Horsley, 1968)
1973p			0	0	1,753	1,227	24
1972			50	4 - 5	1,520	1,064	21
1971			205	13 - 18	1,194	1,038	21
1970			363	23 - 33	1,179	1,025	20
1969			361	25 - 32	1,177	1,024	20
1968			310	22 - 28	958	958	19
1967			358	25 - 32	813	813	16
1966			491	34 - 44	710	710	14
1965		1,981	482	34 - 43	604	604	12
1964		8,832	327	23 - 29	569	569	11
1963		11,836	359	25 - 32	497	497	10
1962		7,321	351	25 - 32	446	446	9
1961		8,861	401	28 - 36	374	374	7
1960	26,619	15,396	497	35 - 45	309	309	6
1959	12,265	7,820	492	35 - 44	288	288	6

Mathieson propylene oxide plant at Brandenburg, Kentucky). The Olin plant has a capacity of 130 million lbs/year, and propylene oxide plants were operated at about 90% of capacity in 1972 (Blackford, 1973b). Using Horsley's (1968) factor, this plant would produce 2.34 million lbs of by-product bis(2-chloroisopropyl)ether a year. The estimated annual discharge of 54,750 lbs does not correlate well with the calculated production. The difference may be attributed to sizable quantities being recovered, although Olin is not listed as a producer of bis(2-chloroisopropyl)ether. Dow Chemical stated that they collect and burn most of their bis(2-chloroisopropyl)ether that is formed as a by-product in their propylene chlorohydrin process, and this may be the explanation for the difference at the Olin Mathieson plant (Otis, 1975). Dow Chemical also indicated that the amount of by-product bis(2-chloroisopropyl)-ether is approximately equal to 2 lbs per 100 lbs of propylene oxide produced and that there are no regular uses or sales for bis(2-chloroisopropyl)ether, except that in the past some material has been exported to Japan. In 1975, there have been no sales to Japan (Otis, 1975).

Other indirect methods are available for estimating the production of some of the other haloethers. For example, the anesthetics, fluroxene ($CF_3CH_2OCH{=}CH_2$) and methoxyfurane ($CHC\ell_2CF_2OCH_3$), are probably produced in relatively small quantities since their application requires only small amounts. A chemical produced by Aldrich Chem. Co., 2,2-dichloroethyl methyl ether, has never appeared in the U.S. Tariff Commission reports and, therefore, is probably produced in extremely low quantities. Similarly, chloromethyl phenyl ether has only recently appeared in the U.S. Tariff Commission reports, thus indicating relatively small amounts. Polychlorinated propyl ether, a compound produced by the Jefferson Chemical Co. in 1963-1966, is no longer being manufactured in sufficient quantity for inclusion in the U.S. Tariff Commission reports (probably not produced at all). 2-chloroethyl vinyl ether is probably synthesized from bis(2-chloroethyl)ether (Lurie, 1965) and, therefore, the vinyl ether production has probably declined similar to the bis(2-chloroethyl)ether production (Union Carbide, the major manufacturer of the vinyl ether, reports that they are no longer making any haloethers.

Both bis(2-chloroethoxy)methane and 2-(2-chloroethoxy)ethyl 2-chloroethyl ether are produced from ethylene chlorohydrin ($C\ell CH_2CH_2OH$). Blackford (1973a) estimated that only about 20 million lbs of ethylene oxide (produced by direct oxidation) are consumed in the production of ethylene chlorohydrin. The chlorohydrin is used as an intermediate in the production of many chemicals besides the ethers, such as indigo and thiodiethyleneglycol. In addition, bis(2-chloroethoxy)methane is principally consumed in the synthesis of polysulfide polymers which are produced in approximately 11.5 million lb quantities (1.5 million, solid elastomers; 10 million, liquid polymers) (Berenbaum and Johnson, 1968).

In 1965, BCME was produced by General Aniline in large enough quantities to be listed in the U.S. Tariff Commission reports, but is no longer being produced. However, in the past, sizable quantities of BCME were produced; for example, between September 1917 and May 1918, 466,000 lbs of BCME were produced by the Germans for use as a war gas and chemical intermediate (Lurie, 1965). CMME, which contains a small amount of BCME (Collier, 1972), is used as a chloromethylating agent in the production of strong-base anion-exchange resins and ionic bactericides (Marceleno and Bierbaum, 1974). The quantity of CMME used is unknown, but is entirely consumed in internal use.

The quantities of haloethers and ethers in general that are imported or exported are considered to be very small due to high transportation costs (U.S. Tariff Commission, 1969). The costs can be attributed to the high volatility of the compounds which results in special shipping considerations.

2. Producers, Major Distributors, Importers, Sources of Imports, and Production Sites

Haloether compounds as a group are somewhat unusual due to the fact that many of the commercially important compounds are only found in large commercial quantities because they are inadvertent by-products of other major commercial products. Thus many of the haloethers are produced at sites and with equipment meant for an entirely different purpose. This is the case with bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether, both of which are found as by-products from the chlorohydrin synthesis of the corresponding epoxide. Complicating this situation is the fact that presently direct oxidation of ethylene to ethylene oxide is economically more attractive than the chlorohydrin route and, therefore, all of the chlorohydrin ethylene oxide facilities have either been closed or converted to propylene oxide. In addition, some manufacturers are beginning to use a direct oxidation process for propylene oxide. Thus the producers and sites of production, at least for some of the major haloethers, appear to be in a continuous state of change.

This continually changing picture is reflected in Table 13 which lists some of the past and present manufacturers of haloethers. Where the information is available, the sites and capacities of the plants are noted in Table 14.

3. Production Methods and Processes

The two major commercial haloethers, bis(2-chloroethyl)-ether and bis(2-chloroisopropyl)ether, are in most instances produced as by-products in the chlorohydrin synthesis of ethylene oxide or propylene oxide. The chlorohydrin approach is economically attractive when a good supply of captive low-cost chlorine and lime or caustic soda as well as a market for the by-products, 1,2-dichloroethane or propane and the haloethers, are available (Schultz, 1965). Both chlorohydrin processes will be reviewed, although chlorohydrin synthesis of ethylene oxide has not been used since 1972.

Ethylene oxide was initially produced commercially by reacting ethylene with hypochlorous acid to yield the ethylene chlorohydrin followed by treatment with base to provide ethylene oxide. The hypochlorous acid can be formed in two ways: (1) by mixing a slurry of hydrated lime with a stream of chlorine to yield the unstable calcium oxychloride which decomposes to give hypochlorous acid and calcium chloride, or (2) by dispersing chlorine in water.

$$\text{(1)} \quad CaO + C\ell_2 \longrightarrow CaC\ell(OC\ell)$$

$$CaC\ell(OC\ell) + C\ell_2 + H_2O \longrightarrow CaC\ell_2 + 2\ HOC\ell$$

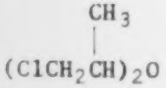
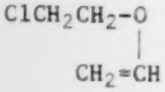
$$\text{(2)} \quad HOH + C\ell_2 \rightleftharpoons HC\ell + HOC\ell$$

Table 13. Past and Present Manufacturers of Haloethers

Chemical Name	bis(2-chloroisopropyl)ether						bis(2-chloroethyl ether						2-chloroethyl vinyl ether		bis-(2-chloroethoxy)methane	2-(2-chloroethoxy)-ethyl 2-chloroethyl ether		chloromethyl methyl ether						2,2-dichloro-1,1-difluoromethyl ether
Structure	$(ClCH_2\overset{CH_3}{CH}-)_2O$						$(ClCH_2CH_2)_2O$						$ClCH_2CH_2OCH{=}CH_2$		$(ClCH_2CH_2O)_2CH_2$	$ClCH_2CH_2O-CH_2$ $ClCH_2CH_2O-CH_2$		$ClCH_2OCH_3$						$Cl_2CHCF_2OCH_3$
Companies	Dow Chemical	Union Carbide	Jefferson Chem.	Mobay Chem.	Olin Mathieson	Wyandotte Chem.	Dow Chemical	Union Carbide	Jefferson Chem.	Buckman Lab.	Olin Mathieson	Wyandotte Chem.	Union Carbide	Alcolac Chem.	Thiokol Chem.	Rohm Haas	Union Carbide	Stauffer	Rohm & Haas	Hooker Chem.	Eastman Kodak	Unidentified Manufacturer	Dow Chemical	Dow Chem.
Personal Contact (1975)	X	/	-	-	-	-	/	/	-	-	-	-	/	-	-	/	/	-	X	-	-		X	X
Stanford Research Institute Directory of Chemical Producers (1974)	X	X	/	/	/	/	X	X	/	X	/	/	X	/		/	/	X	/	/	/			X
U.S. Tariff Commission Synthetic Organic Chemicals																								
1972	X	/	/	X	/	/	X	/	/	/	/	/	X	X	X	/	/	/	X	/	/	/		X
1971	X	/	/	/	/	/	X	/	/	/	/	/	X	X	X	X	/	/	X	X	/	/		X
1970	X	/	/	/	X	/	X	/	/	/	/	/	X	/	X	/	/	/	X	X	/	/		X
1969	X	/	/	/	/	/	X	X	/	/	/	/	X	/	X	/	/	X	X	X	/	/		X
1968	X	/	/	/	/	/	X	X	/	/	/	/	X	/	X	/	/	/	X	X	/	/		X
1967	X	/	/	/	/	/	X	X	/	/	/	/	X	/	X	/	/	/	X	X	/	/		X
1966	X	/	/	/	/	/	X	X	/	/	/	/	X	/	X	/	/	/	X	X	/	/		X
1965	X	/	/	/	/	/	X	X	X	/	X	/	X	/	X	/	/	/	/	X	/	X		X
1964	X	/	/	/	/	X	X	X	X	/	X	/	X	/	X	/	X	/	/	X	/	X		X
1963	X	/	/	/	/	X	X	/	X	/	X	X	X	/	X	/	X	/	/	X	/	X		X
1962	X	/	/	/	/	X	X	/	X	/	X	X	X	/	X	/	X	/	/	X	X	X		/
1961	X	/	X	/	/	X	X	/	X	/	X	X	X	/	X	/	X	/	/	X	X	X		/
1960	X	X	X	/	/	X	X	X	X	/	X	X	X	/	X	/	X	/	/	X	X	X		/
1959	X	/	/	/	/	X	/	X	X	/	X	/	X	/	X	/	X	/	/	X	X	X		/

X = manufacturer
/ = not a manufacturer
- = not contacted

Table 14. Capacities and Production Sites of Haloether Manufacturers (SRI, 1974; Blackford, 1973a,b).

Chemical	Company	Location	Capacity (10^6 lbs) (in terms of oxide produced by chlorohydrin route)	Remarks
$(ClCH_2CH_2)_2O$	Buckman Labs.	Cadet, MO	---	
		Memphis, TN	---	
	Dow Chemical	Freeport, TX	200	Converted to propylene oxide (1972)
	Union Carbide	Institute and South Charleston, WV	---	No longer produces this compound
 $(ClCH_2\overset{CH_3}{\overset{\vert}{C}H})_2O$	Dow Chemical	Freeport, TX	600	
		Plaquemine, LA*	220	
	Union Carbide	South Charleston, WV	220	Closed May, 1972
	BASF Wyandotte	Wyandotte, MI*	175	
	Jefferson Chem.	Port Neches, TX*	150	
	Olin Corp.	Brandenburg, KY*	130	May have closed in 1974
 $ClCH_2CH_2\text{-}\underset{CH_2=CH}{\underset{\vert}{O}}$	Union Carbide	Institute and South Charleston, WV		No longer produces this compound
$ClCH_2OCH_3$	Stauffer	Edison, NJ		
	Rohm and Haas	Philadelphia, PA		
	Diamond Shamrock	Redwood City, CA		
	Dow Chemical	Midland, MI		
$(ClCH_2CH_2O)CH_2$	Thiokol Corp.	Moss Point, MS		
Cl_2CHOCH_3	Aldrich Chem.	Milwaukee, WI		
$CHCl_2CF_2OCH_3$	Dow Chemical	Midland, MI		
$CF_3CH_2OCH=CH_2$	Airco Inc.	Cleveland, OH		

* Not listed as manufacturing site in SRI _Directory of Chemical Producers_, 1974.

Two major by-products, 1,2-dichloroethane and bis(2-chloroethyl)ether, which are formed during the chlorohydrin formation are depicted below.

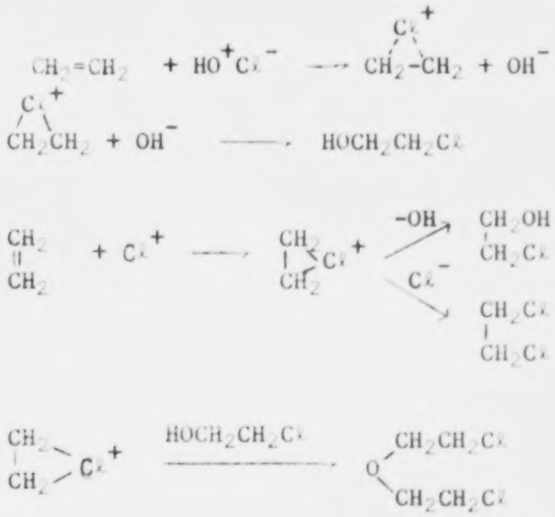


Figure 7. Formation of Bis(2-chloroethyl)ether During Chlorohydrin Synthesis of Ethylene Oxide

From the equations above, it can be seen that the amount of 1,2-dichloroethane formed is dependent upon the ethylene and chlorine gas concentrations and that the amount of ether formed is dependent upon the ethylene chlorohydrin concentration. In most chlorohydrin processes ether formation is minimized by avoiding high chlorohydrin concentrations (Lichtenwalter and Riesser, 1964).

A typical chlorohydrin process ethylene oxide plant is depicted in Figure 8. The bis(2-chloroethyl)ether would be found with the ethylene dichloride noted in the diagram. Table 15 notes the quantities of reactants consumed and products formed in the production of 1000 lbs of ethylene oxide in 80% yield.

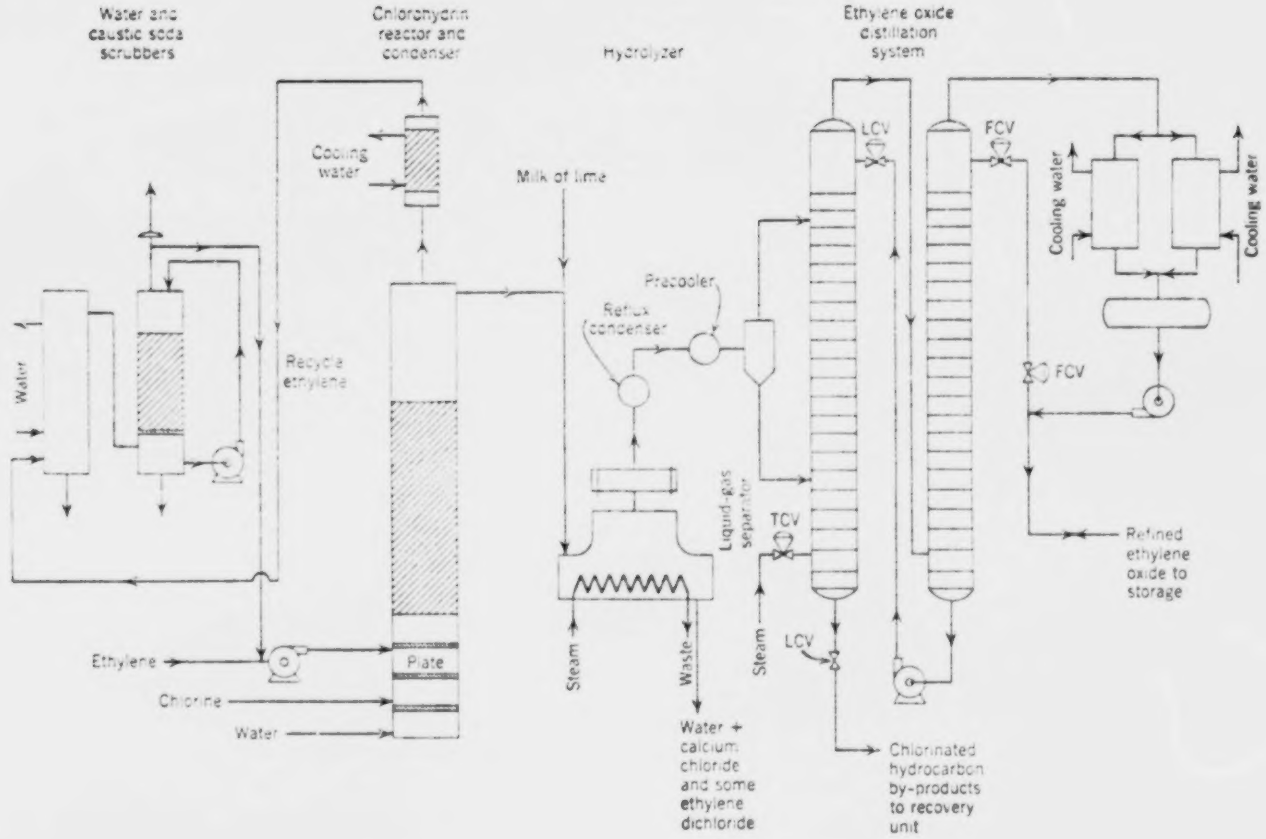

Water and caustic soda scrubbers
Chlorohydrin reactor and condenser
Hydrolyzer
Ethylene oxide distillation system
Cooling water
Milk of lime
Recycle ethylene
Water
Precooler
Reflux condenser
LCV
FCV
Cooling water
Cooling water
FCV
Liquid-gas separator
TCV
Plate
Ethylene
Chlorine
Water
Steam
Waste
Steam
LCV
Water + calcium chloride and some ethylene dichloride
Chlorinated hydrocarbon by-products to recovery unit
Refined ethylene oxide to storage

Fig. 8. Chlorohydrin process for manufacturing ethylene oxide (Schultze, 1965)
LEGEND: FCV, flow-control-valve; LCV, liquid-control valve; TCV, temperature-control valve.

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Table 15. Reactants and Products of the Ethylene Oxide Chlorohydrin Process (Schultze, 1965)

Reactants

Compound	Quantity (lbs)
Ethylene	800
Chlorine	2000
Lime (as CaO)	1600

Products

Compound	Quantity (lbs)
Ethylene oxide	1000
Calcium chloride	3200
1,2-dichloroethane	100-150
Bis(2-chloroethyl)ether	70-90
Acetaldehyde	5-10

As noted earlier, ethylene oxide is no longer commercially produced by the chlorohydrin route. This is basically due to the fact that the direct oxidation process has lower operating costs, although the capital investment for direct oxidation is 50% higher than the chlorohydrin process. (Schultze, 1965)

Bis(2-chloroethyl)ether can also be produced in high yield by saturating an aqueous solution of ethylene chlorohydrin with chlorine and ethylene or by heating ethylene chlorohydrin with sulfuric acid (Tschamler, 1950).

The propylene chlorohydrin route to propylene oxide still enjoys a competitive economic position. Approximately 70% of the capacity is still based on chlorohydrination as opposed to peroxidation (direct oxidation). The switch to the direction oxidation route to ethylene oxide has freed paid-up ethylene chlorohydrin facilities for propylene chlorohydrin manufacture, "posing stiff competition, indeed for direct propylene oxide processes" (Sittig, 1968). This is especially true considering that chlorohydrin plants for ethylene oxide are readily converted to propylene oxide in only 24-36 hr (Lapkin, 1965).

As with ethylene chlorohydrin, propylene chlorohydrin is formed by reacting hypochlorous acid with propylene. However, unlike the ethylene chlorohydrin process, two chlorohydrins are possible with propylene chlorohydrin, and as a result three ethers may be formed (see Figure 9).

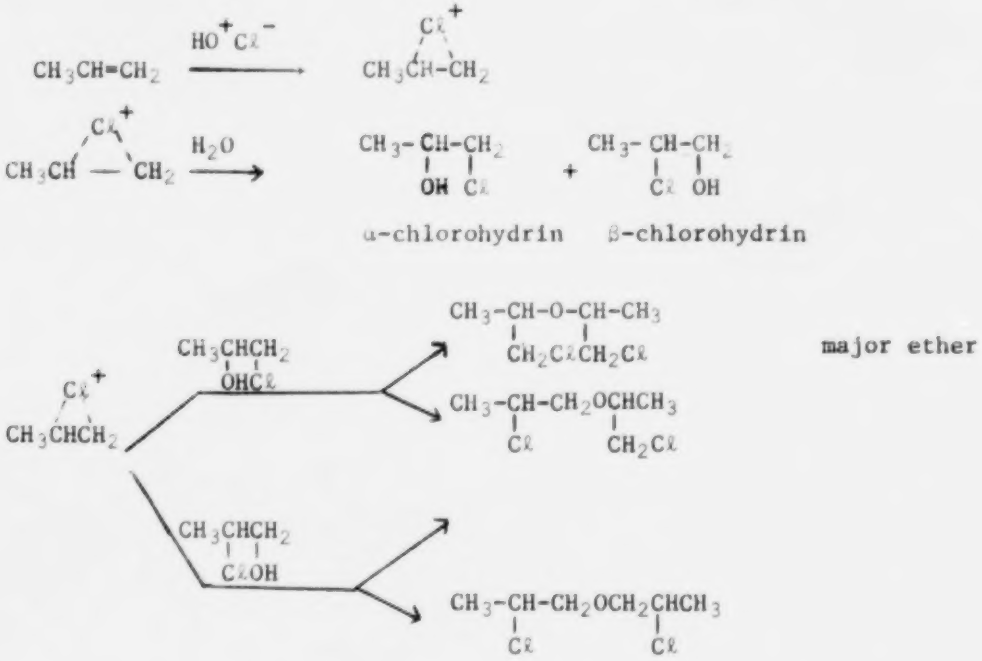

Figure 9. Formation of Bis(2-chloroisopropyl)ether and Related Ethers During Chlorohydrin Synthesis

The α-chlorohydrin is the major product, because of the stability of the secondary carbon atom, but the isomer ratios has been reported to vary from 3:1 to 9:1 (Lapkin, 1965). The major ether isomer is the bis(2-chloroisopropyl)ether. As with the production of ethylene chlorohydrin, a major by-product, which is formed in larger quantities than the ethers, is the propylene dichloride.

A typical chlorohydrin reactor for manufacturing propylene oxide is depicted in Figure 10. The haloethers would be found at the same locations as crude propylene dichloride: (1) in the chilled caustic soda wash of unreacted gases (sometimes a partial condenser is used to remove propylene dichloride and bis(chloroisopropyl)ether, Horsley, 1968) and (2) in the aqueous effluent from the steam heated flash hydrolyzer.

Yields for hypochlorination of propylene are frequently in the neighborhood of 90%, although the yield can be improved by reducing the chlorohydrin concentration to less than 4% (Lapkin, 1965). For every ton of oxide produced, 40 tons of aqueous effluent are generated (Lapkin, 1965) which can present a major disposal problem. Depending upon the location and local ordinances, the effluent may be simply discharged or it may be treated by a sewage works before release. Table 16 shows the ratio of reactants to products in a typical propylene chlorohydrin plant.

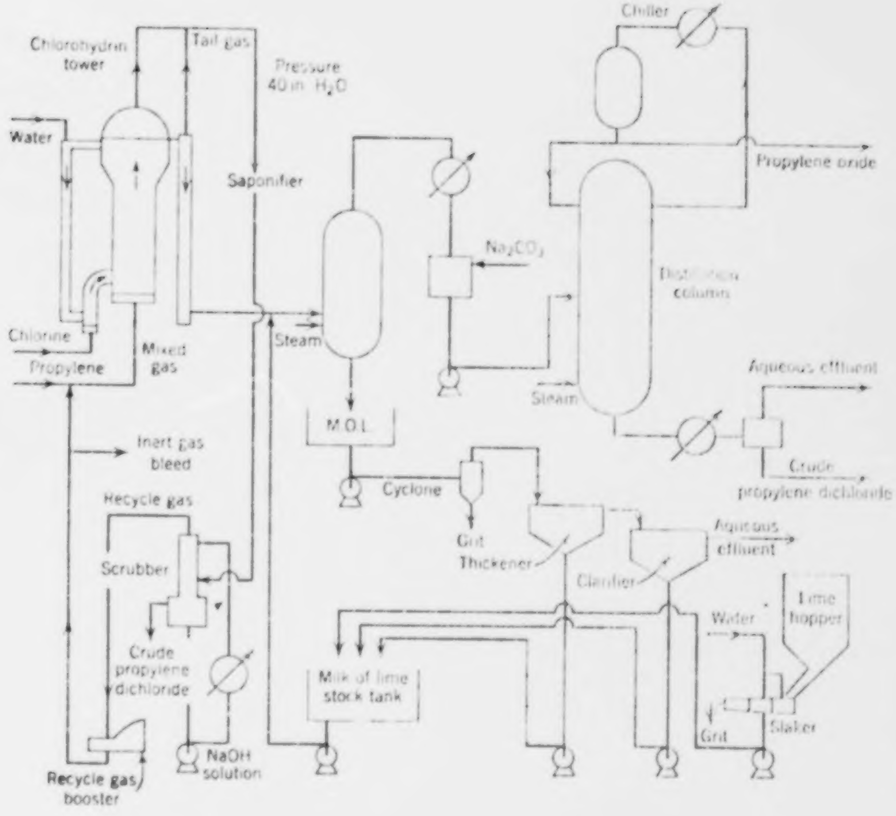

Figure 10. Diagram of a Typical Chlorohydrin Propylene Oxide Plant (Fyvie, 1964)

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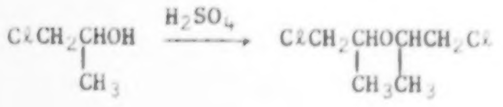
Table 16. Products and Reactants of a Typical Propylene Chlorohydrin Plant (Horsley, 1968)

Reactants	lb	moles
propylene	94	2.24
chlorine	159	2.24
lime (as CaO)	109	1.95
Products		
propylene oxide	100	1.72
propylene chloride	9	0.0796
dichloropropyl ethers	2	0.0117
$CaC\ell_2$ brine (100% basis)	215	1.95

As with bis(2-chloroethyl)ether, bis(2-chloroisopropyl)-ether can also be prepared by dehydration with sulfuric acid.



$$C\ell CH_2\underset{CH_3}{\underset{|}{C}}HOH \xrightarrow{H_2SO_4} C\ell CH_2\underset{CH_3}{\underset{|}{C}}HO\underset{CH_3}{\underset{|}{C}}HCH_2C\ell$$

Information on the commercial synthesis of the other haloethers is not very detailed. The following will review some of the processes that may be used in industry. However, although it is likely that the basic chemistry may remain the same, the equipment and handling may change considerably.

While CMME can be made by a variety of approaches including direct chlorination of dimethyl ether (Hake and Rowe, 1963; Lurie, 1965), the most frequently used technique is to pass gaseous hydrogen chloride through a heated solution of formaldehyde and methanol (Hake and Rowe, 1963; Summers, 1955; Fieser and

Fieser, 1967; VEB Farbenfabrik Wolfen, 1967a,b; Cherepanova and Chereva, 1961). In this process, small amounts of BCME (several percent) are also produced (Collier, 1972).

$$HCHO + CH_3OH \xrightarrow{HCl} ClCH_2OCH_3$$

In the past, CMME was produced in batches in loosely covered reaction kettles (Figueroa et al., 1973). However, because of occupational exposure, CMME is now generated in batches in completely enclosed rooms (Rohm and Haas, personal communication, 1975). The ether that is formed is reacted with the polymer chain and any remaining ether is destroyed by hydrolysis workup. The source of formaldehyde can be paraformaldehyde, poly(oxymethylene), or tris(oxymethylene). German patents by VEB Farbenfabrik Wolfen (1967a,b) suggest using a countercurrent reactor and an excess of paraformaldehyde (the latter increased the yield). Yields can also be increased by passing a stream of inert gas (N_2, air, or preferably HCl) through the aqueous waste acid and recovering the BCME from the gas stream by cooling (Bachman et al., 1966).

The methods for preparing BCME have been reviewed by Buc (1956). For laboratory purposes, the most convenient procedure is the reaction of paraformaldehyde and chlorosulfonic acid (source of hydrochloric acid).

$$2\ CH_2O + 2\ ClSO_3H + H_2O \longrightarrow (ClCH_2)_2O + 2\ H_2SO_4$$

Evidence also suggests that BCME is formed whenever formaldehyde and a chloride ion source are present (Frankel et al., 1974; Marceleno and Bierbaum, 1974; Marceleno et al., 1974a,b).

At the present time, the exact path of formation for BCME using formaldehyde and HCl is unknown. Solomon (1975) suggested that it can take path a (see Figure 11) which involves the intermediacy of a formaldehyde dimer $HOCH_2OCH_2^+$ or path b which involves the intermediate formation of chloromethanol. He quoted Olah and Yu (1975) as demonstrating that the hydroxycarbonium ion gives chloromethyl alcohol with HCl and that this exists as an intermediate in acid medium as the chloromethyloxonium ion. Combination of the species with protonated formaldehyde followed by attack of chlorine leads to the direct formation of BCME. Although both paths may be involved in the formation of BCME, path b is likely to predominate. These and other processes are presently under investigation by the National Institute for Occupational Safety and Health (NIOSH) through contract with the Bendix Corporation which is also evaluating existing BCME analytical and sampling protocols.

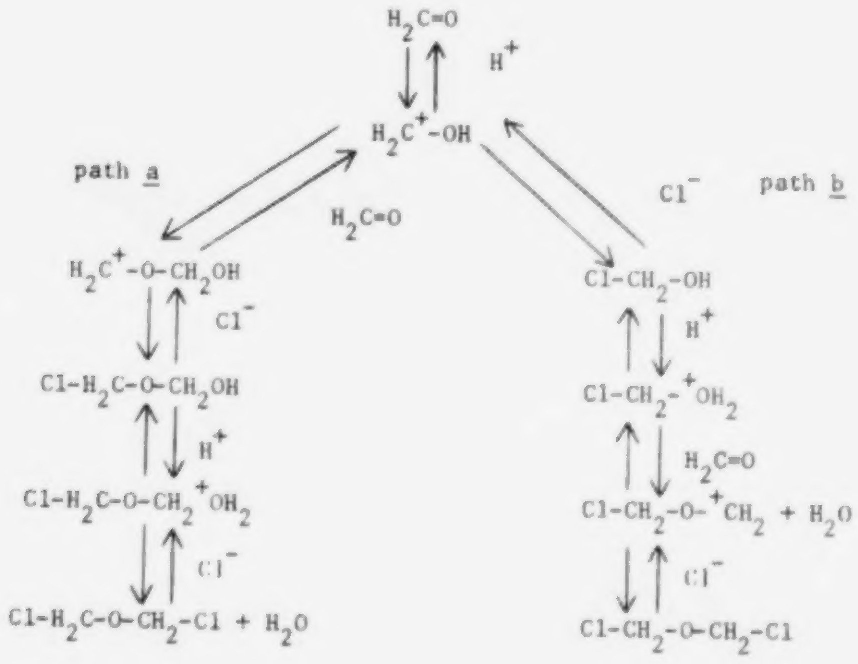


Figure 11. Suggested Mechanism for the Formation of Bis(chloromethyl)ether

The synthetic route used for commercial synthesis of methoxyfurane ($CHC\ell_2CF_2OCH_3$) is unknown. However, a patent by Hudlicky (1965) suggests the following approach.

$$CH_3OH + F_2C{=}CC\ell_2 \xrightarrow[\text{or KOH}]{CH_3ONa} CH_3OCF_2CHC\ell_2$$

In order to synthesize 2-chloroethyl vinyl ether, a dehydrochlorination approach from the bis(2-chloroethyl)ether may be used (Lurie, 1965).

$$C\ell CH_2CH_2OCH_2CH_2C\ell \xrightarrow[\text{NaOH}]{\text{hot flake}} C\ell CH_2CH_2OCH{=}CH_2$$

Bis(2-chloroethoxy)methane has been produced for many years for consumption in polysulfide polymers. It is prepared by condensation of ethylene chlorohydrin with anhydrous formaldehyde. An azeotroping agent is used to drive the reaction to completion by removing the water formed in the process (Berenbaum and Johnson, 1968).

$$2\ C\ell CH_2CH_2OH + CH_2O \longrightarrow C\ell CH_2CH_2OCH_2OCH_2CH_2C\ell + H_2O$$

4. Market prices

Recent information on the market price of commercial haloethers is not available. However, some historical information is available on bis (2-chloroethyl)ether and bis(2-chloroisopropyl)ether. Lurie (1965) reported that the ethers, when shipped in 55 gallon drums, were sold for $0.13-15/lb. The price of bis(2-chloroethyl)ether during the early 1960's is listed in Table 17.

Table 17. Price of Bis(2-chloroethyl)ether
(U.S. Tariff Commission)

Year	1959	1960	1961	1962	1963	1964	1965
Price($/lb)	0.07	0.02	0.02	0.02	0.02	0.02	0.09

Table 18 lists the prices of a variety of haloethers when they are sold in laboratory quantities. Although the prices are far removed from the value of large commercial quantities of the chemicals, they are somewhat indicative of the relative value.

Table 18. Prices of Haloethers (Aldrich, 1975-76)

Ether	Price $
Bis(2-chloroethyl)ether	6.00/500g
Bis(2-chloroisopropyl)ether	15.75/4kg
2-Chloroethyl vinyl ether	24.90/500g
Chloromethyl methyl ether	17.35/500g
α,α-Dichloromethyl methyl ether	23.50/100g

5. Market Trends

Use of haloethers in large commercial quantities appears to be declining. Bis(2-chloroethyl)ether, which was produced in 26 million lbs in 1960, is no longer produced in large quantities due to the change over to direct oxidation production of ethylene oxide. Direct oxidation is also beginning to infringe on chlorohydrin synthesis of propylene oxide, thus leveling off the availability of by-product bis(2-chloroisopropyl)ether. Use of CMME in the production of ion exchange resins seems to be continuing, although large investments are being incurred in order to prevent occupational exposure to the chemical (Dr. E. Beavers, Rohm and Haas, cited in Hricko and Pertschuk, 1974). The anesthetics will probably continue to be used in small quantities and the acetal, bis(2-chloroethoxy)methane, will continue to be consumed as the principal monomer in the production of polysulfides.

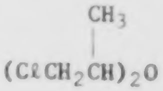
B. Uses

1. Major Uses

The major commercial applications of haloethers can be grouped into three general areas: (1) anesthetics - usually fluorinated ethers, (2) chemical intermediates - mostly the α-haloethers because of their reactivity, and (3) solvent use - usually the β-haloethers due to their stability, low price, high boiling points, and unique solubility properties. These uses are summarized in Table 19.

The two commercial haloethers which contain fluorine substituents are exclusively used as general anesthetics. Fluroxene (CF_3CH_2-$OCH{=}CH_2$) is

Table 19. Major Uses of Haloethers

Compound	Structure	Use
Fluroxene	$CF_3CH_2OCH=CH_2$	General anesthetic
Methoxyflurane	$CHC\ell_2CF_2OCH_3$	General anesthetic
Bis(2-chloroethoxy)methane	$(C\ell CH_2CH_2O)_2CH_2$	Principal monomer in the production of polysulfides
Chloromethyl methyl ether	$C\ell CH_2OCH_3$	Chloromethylating agent for anion exchange resins, membranes, and other aromatic products
Bis(2-chloroethyl)ether	$(C\ell CH_2CH_2)_2O$	Dewaxing agent for lubricating oils - Solvent, pentrant, and wetting agent in the textile industry - Chemical intermediate
Bis(2-chloroisopropyl)-ether	 $(C\ell CH_2\overset{\overset{CH_3}{\vert}}{C}H)_2O$	Solvent in paint and varnish removers, spotting agents, and cleaning solutions - Soap additive in textile industry -Chemical intermediate

usually administered by inhalation using open, semi-closed, or closed techniques (Ohio Medical Products, 1972). It has the advantage of rapid induction of anesthesia at comparatively low levels in inspired air and yet recovery is rapid due to low solubility of the compound in blood. Methoxyflurane ($CHC\ell_2CF_2OCH_3$) is an excellent volatile anesthetic which has a slow induction time, but good relaxation of skeletal musculature (Krantz, 1963).

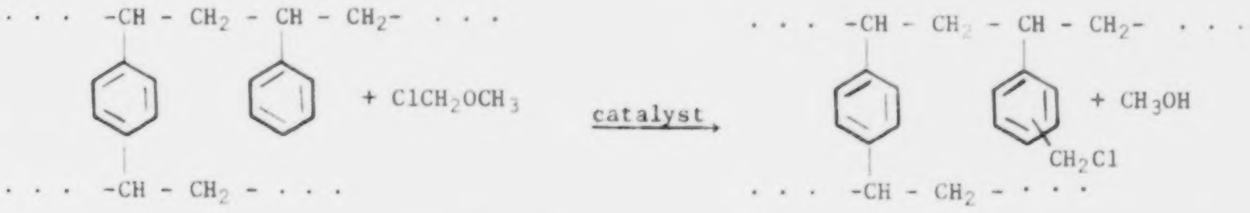
Bis(2-chloroethoxy)methane ($ClCH_2CH_2OCH_2OCH_2CH_2Cl$) finds its major application as the principal monomer in polysulfide polymers (Berenbaum and Johnson, 1968). The chemical is manufactured by Thiokol at their Moss Point, Mississippi, plant and is totally consumed in the production of polysulfides. These specialty polymers are used as room temperature curing liquid polymers in the sealant and adhesives market because of their good solvent resistance, good low-temperature performance, and good weathering and ozone resistance. There is also a limited market (~1.5 million lbs/year, 1968) for the solid elastomers in printing rolls, paint spray hoses, and solvent resistant gaskets and diaphragms. The polymers are formed by polycondensation of the bis(2-chloroethoxy)methane with an aqueous polysulfide solution. Frequently, 1,2,3-trichloropropane is added for cross-linking and in some instances bis(4-chlorobutoxy)methane or bis(4-chlorobutyl)ether are used in minor amounts to improve low temperature performance (Berenbaum and Johnson, 1968).

Since the α-haloethers are very reactive, they constitute a useful class of intermediates (Lurie, 1965; Summers, 1955). Of this group of chemicals, CMME is the most important commercially. It is generally used as a chloromethylating agent in many synthetic processes, the most important being the chloromethylation step in the production of strong-base anion exchange resins. The companies and their plant locations which use CMME for producing ion exchange resins are listed in Table 20.

Table 20. Principle Ion Exchange Resin Producers
(Wheaton and Seamster, 1966)

Company	Location	Trademark
Diamond Shamrock	Redwood City, Calif.	Dualite
Dow Chemical Co.	Midland, Mich.	Dowex
Rohm and Haas Co.	Philadelphia, Pa.	Amberlite
Ionac Chemical Corp.	Birmingham, N.J.	Ionac

The strong-base anion exchange resins are made by attaching a quarternary ammonium group to a poly(styrene-divinylbenzene)matrix. The chloromethylation is accomplished by placing the copolymer beads in the ether (beads become fully swollen) with a Friedel-Crafts condensation catalyst (e.g. $AlCl_3$, $SnCl_4$, $FeCl_3$ or $ZnCl_2$).



the chloromethylated polymer is then reacted with various tertiary amines to form the quaternary ammonium salt.

$$-CH_2Cl + NR_3 \longrightarrow -CH_2N\overset{+}{R}_3Cl^-$$

The two tertiary amines which are used most commonly are trimethylamine (Amberlite IRA-400, Amberlite IRA-401, Amberlite IRA-402, Amberlite IRA-900, Duolite A-101-D, Duolite ES-111, Dowex 1, Dowex 11, Dowex 21K, and Ionac A-540) and dimethylethanolamine (Amberlite IRA-410, Amberlite IRA-911, Dowex 2, Duolite A-102-D, Ionac A-542, and Ionac A-550) (Wheaton and Seamster, 1966).

The commercial uses of the two β-haloethers, bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether, are extremely similar. The ethyl ether, which is frequently identified by the Union Carbide tradename Chlorex (Lurie, 1965), was first recognized as an effective, low-cost solvent (Fairhall, 1949). In the past, its principal use was as a dewaxing agent for lubricating oils because it is a powerful solvent for naphthenic components but a poor solvent for paraffin components (Fairhall, 1949; Jacobs and Scheflan, 1953; Pollard and Lawson, 1955; Mervart et al., 1960). After separation, the solvent is recovered by distillation (Pollard and Lawson, 1955). The chloroethyl ether has also been used to separate butadiene from butylene (Lurie, 1965). The second major use of bis(2-chloroethyl) ether is in the textile industry as: (1) a solvent to remove paint and tar brand marks from raw wool and oil and grease spots from cloth, and for use in scouring and fulling soaps where low solvent loss at elevated temperatures is required (sometimes used to replace sodium hydroxide in kier boiling), and (2) as a wetting agent and penetrant in combination with diethylene glycol, sulphonated oils, etc. (Browning, 1953; Jacobs and Scheflan, 1953; Allen, 1956). The compound generally is a good solvent for tars, fats, waxes, oils, resins, pectins, and will dissolve cellulose esters when used with 10-30% ethanol (Fife and Reid, 1930). The ether also finds some application as a chemical intermediate. The quantities of bis-(2-chloroethyl)ether used in these applications is unknown but is expected to be very low based on the fact that the two major manufacturers (Dow Chemical and Union Carbide) are no longer producing the compound.

Bis(2-chloroisopropyl)ether is also an excellent solvent and extractant for fats, waxes, and greases and finds some use as a cleaning and spotting agent as well as an additive to paint and varnish removers (Hake and Rowe, 1963; Lurie, 1965). However, its use in dewaxing lubricating oils is not as common as it is with Chlorex. Similar to the chloroethyl ether, the chloroisopropyl ether is used to assist the action of hot soap solutions used in textile processes. The ether is also used as a chemical intermediate where a more oil soluble product than formed with the chloroethyl ether is desired (dyes, resins and pharmaceuticals - Hake and Rowe, 1963).

2. Minor Uses

A number of miscellaneous applications of haloethers have been reported in the literature. These are summarized in Table 21 with the appropriate references. Some of the compounds in Table 21 were not discussed in the previous section because they are used in such small quantities.

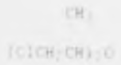
3. Discontinued Uses

The available information on the uses of haloethers is not very up-to-date or quantitative. However, one compound that is being used less and less is bis(2-chloroethyl)ether. The two major manufacturers no longer make the chemical, and the chlorohydrin process to ethylene oxide, which produces bis(2-chloroethyl)ether as a by-product, has not been used since 1972. When bis(2-chloroethyl)ether was a relatively cheap, unwanted by-product of another large commercial process, it had numerous applications. However, now that the compound is relatively expensive, it probably finds little application, especially in its solvent applications. Even when it was relatively inexpensive, Mervart et al. (1960) concluded that aqueous acetone was less expensive than bis(2-chloroethyl)-ether for the isolation of 1,3-butadiene from 1-butene.

4. Projected or Proposed Uses

Table 21 lists a number of minor applications of haloethers that might be potential major uses. In many cases, the more recent references are patent applications and, therefore, possible growth applications. Of the compounds cited, 2-chloroethyl vinyl ether appears to have the greatest potential for growth. Its successful use as a copolymer would substantially increase the amount of compound being produced.

Table 21. Minor Uses of Haloethers

Compound	Use	Reference
$(ClCH_2CH_2)_2O$	1% H_2O suspension-insecticidal soil fumigant	Hake and Rowe (1963)
	dry-cleaning agent	
	insecticide, acaricide, and soil fumigant	Lurie (1965)
	gasoline additive to scavenge lead deposits	
	synthesis of morpholine, N-substitute morpholine, and divinyl ethyl	
	synthesis of plasticizers, synthetic rubbers, pharmaceuticals and resins	Fairhall (1949)
	aqueous solution - soil disinfectant against Japanese beetle grubs and wire grubs	
	synthesis of amino ethers (inhibitors, antioxidants, and antiknock compounds)	Fife and Reid (1930)
	one of three ways to synthesize morpholine	Nieneker (1967)
	synthesis of 4-aminomorpholine (reaction with hydrazine)	Farrar (1956)
	synthesis of divinyl ether	Ruigh and Major (1931)
	used with 1,3 dichloropropene and 1,2-dichloropropane in microcapsules as a nematocide	Siebel (1972)
	used to prepare good impact resistance styrene copolymers	Ihouchi (1974)
	synthesize β-(β-chloroethoxy)phenetole analogues of DDT	Omarov *et al.* (1966)
	synthesis of surfactants	Anon (1975)
 $(ClCH_2\overset{CH_3}{C}H)_2O$	low-temperature dewaxing of oils	Seleznev and Stepuro (1962)
	used in wood preservative formulation with pentachlorophenol Na salt	Ishii *et al.* (1974)
$(ClCH_2CH_2CH_2CH_2)_2O$	used in minor amounts as monomer in polysulfides to improve low-temperature performance	Berenbaum and Johnson (1968)
$ClCH_2CH_2OCH{=}CH_2$	oil and water repelling copolymer for cotton	Kirimoto and Hayashi (1974)
	copolymer with acrylic elastomers	Kaendler *et al.* (1973)
	copolymer beads	Cohen (1970)
$ClCH_2OCH_3$	synthesis methoxymethyl ethers of phenols	Fieser and Fieser (1967)
	crosslinking polystyrene	Peyrot (1971)
	surface treatment of vulcanized rubber to increase adhesion of epoxy resin or polyurethane elastomers	Honda *et al.* (1974)
$ClCH_2OCH_2Cl$	crosslinking cellulose	Guthrie and Heinzelman (1972)
	preparation of three-block styrene-butadiene-styrene polymers	Bebb and Carr (1971)
	surface treatment of vulcanized rubber to increase adhesion of epoxy resin and polyurethane elastomers	Honda *et al.* (1974)

5. Possible Alternatives to Use

The uses of haloethers can be divided into two broad categories: (1) applications that use the chemicals as intermediates, and (2) applications that make use of the physical properties (e.g., solubility) of the chemicals. Alternatives to the latter uses are easier to find since other chemicals can often be used. However, with chemical intermediate applications, few alternatives are possible unless a new synthetic route is developed.

Of the major haloethers (Table 19), CMME and bis(2-chloroethoxy)-methane are used exclusively as chemical intermediates. CMME is used in the manufacture of anion-exchange resins. The resins find applications in deionizing water and as a method of separation in many industrial chemical processes (e.g., recovering uranium from sulfuric acid leach liquors) (American Chemical Society, 1973). The occupational difficulties encountered with CMME (see Section III-C-1, p. 86) have provided considerable incentive to review alternative synthetic approaches. Whether possible alternatives were seriously considered is unknown, but the fact that the anion exchange resins are still being produced by the CMME route even with costly modifications of the production facilities suggests that alternatives to this use of CMME are limited. However, an alternative approach to the benzyl chloride function through side-chain chlorination of polyvinyltoluene has been reported (McMaster _et al_., 1953).

Bis (2-chloroethoxy)methane is the principal monomer in the production of polysulfides. The polysulfides are commercially modest, specialty polymers which are used mostly for their solvent resistance. Other dihalide monomers might be used, but whether they would provide the same desired properties is unknown. Other compounds such as silicones might be used, but such alternatives require considerably more review than is possible here.

The two fluorinated haloethers are used exclusively as general inhalation anesthetics. Other inhalation anesthetics that might be used as alternatives include nitrous oxide, ether, chloroform, ethylene, cyclopropane, vinyl ether, ethyl vinyl ether, ethyl chloride, trichloroethylene and halothane ($CF_3CHBrCl$) (Krantz, 1963).

The two remaining commercial haloethers, bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether, are mostly used as solvents. The uniqueness of their solvent properties is difficult to assess, but it appears, at least for bis(2-chloroethyl)ether, that its use was more dependent upon its price than on its solubility properties. Presently, little bis(2-chloroethyl)ether is used in solvent applications, so some alternatives must have been devised. As noted earlier, Mervart et al. (1960) concluded that aqueous acetone was cheaper for the separation of 1,3-butadiene from 1-butene. The chemical intermediate applications of the two compounds would be much more difficult to replace. Contamination from the chemical intermediate use of bis(2-chloroethyl)ether may be quite significant (Anon., 1975).

C. Environmental Contamination Potential

1. General

The potential for environmental contamination from haloethers varies considerably with the different compounds and applications. The greatest potential appears to be from the inadvertent production of these chemicals in other industrial processes such as the chlorohydrin processes. These potential sources will be discussed in greater detail in the following subsections. Other sources are also briefly discussed when information is available.

2. Production

CMME containing a few percent of BCME is produced by Rohm and Haas in a plant building where the chemicals are isolated from the workers by closed partitions and the area is maintained at negative pressure. A trailer located just outside the building routinely draws air samples from eight different locations in the plant. This monitoring assures that the workers are not exposed to more than 1 ppb of BCME (limits of detection of the dual gas-chromatographic technique). In addition, "procedures have been developed for decontaminating all waste streams, both gaseous and liquid, that might contain bis-CME" and these procedures have been instituted in the Rohm and Haas Philadelphia plant (statement of Dr. E. Beavers, Rohm and Haas, cited in Hricko and Pertschuk, 1974). The above information is all that was available in the reviewed literature. Whether the plants and analytical sampling systems are similar in other companies that produce CMME (i.e., Stauffer, Diamond Shamrock, and Dow Chemical), is unknown.

3. Transport and Storage

The quantities of haloethers lost during transport and storage are unknown. CMME and BCME are produced and consumed at the same location and, therefore, no loss during transport and storage is likely. Similar reasoning applies to bis(2-chloroethoxy)methane which is produced and probably used at the same plant by Thiokol in the synthesis of polysulfides. Bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether are available in 55-gal drums (Lurie, 1965), and fluroxene ($CF_3CH_2OCH=CH_2$) is packaged in amber bottles containing 125 ml (Ohio Medical Products, 1972).

4. Uses

The possibility of loss of CMME and traces of BCME during their use as chloromethylating agents in the production of anion exchange resins seems rather remote. After the chloromethylation step, the polymer is reacted with a tertiary amine in a polar solvent such as water (Wheaton and Seamster, 1966). The half-lifes of these two compounds in aqueous systems is a matter of seconds (see Section I-B-2, p.11, on hydrolysis) and, therefore, all the material should be destroyed. Rohm and Haas has ruled out the possibility of BCME remaining in the anion-exchange resins by radiotracer experiments with C^{14} BCME (statement of Dr. E. Beavers, Rohm and Haas, cited in Hricko and Pertschuk, 1974).

In contrast to the α-chloroethers, some of the other chloroethers are likely candidates for release to the environment. When bis(2-chloroethyl)ether is used to separate paraffins from lubrication stocks, the solvent is recovered by distillation. In order to completely strip the solvent, live steam is introduced into the evaporator (Pollard and Lawson, 1955). This contact with water could be a source of water contamination. Two β-chloro compounds, bis(2-chloroethoxy)-methane and bis(2-chloroethyl)ether, have been detected in the treated wastes from a synthetic rubber plant (140 mg/ℓ and 0.16 mg/ℓ, respectively) (Webb et al., 1973). In addition, just recently bis(2-chloroethyl)ether has been detected in the effluent from the Rohm and Haas Philadelphia plant (Anon., 1975). Rohm and Haas acknowledged that they were discharging up to 135 lbs/day of the intermediate, which is used in industrial surfactant production.

5. Disposal

No information was located on the disposal procedures for haloethers. However, with the α-chloroethers, hydrolysis is an obvious choice because of the rapid rate of reaction.

6. Potential Inadvertent Production of Haloethers in Other Industrial Processes

Because BCME is a potent carcinogen, considerable attention has been focused on possible inadvertent production of the chemical in various industrial processes. BCME is produced in the laboratory by reacting formaldehyde with hydrochloric acid (Buc, 1956). However, until 1973, no one considered whether BCME would be formed when formaldehyde and hydrochloric acid were present at low concentrations.

The Rohm and Haas Company (Anon., 1973) first announced that BCME can form spontaneously in ordinary humid air. In a detailed study, Frankel et al. (1974) studied a variety of concentrations of hydrogen chloride and formaldehyde at room temperature and 40% relative humidity. The amount of BCME formed for each concentration is presented in Table 22. The specificity and sensitivity of the analytical methods used by Frankel et al. (1974) and in other studies described in this section are reviewed in Section II-E, p. 65.

Table 22. Amount of BCME Formed at 40% Relative Humidity and 26°C at Various $CH_2O/HC\ell$ Concentrations (Frankel *et al.*, 1974)

(Reaction times, 12-24 hr.)

$CH_2O/HC\ell$, ppm	BCME, ppb
4000/40,000	5000
1000/10,000	730
1000/1000	130
300/300	23
100/100	3
20/20	<0.5 (limit of detection)

Kallos and Solomon (1973) of Dow Chemical also conducted a similar study on the formation of BCME in $HCHO/HC\ell$ simulated atmospheres. They used both glass and Saran reactors, as did Frankel *et al.* (1974), and evaluated different commercial sources of formaldehyde and hydrogen chloride. The yields of BCME in this study were much less (largest - 48 ppb for 3000/10,000 ppm $HCHO/HC\ell$) than those obtained by Frankel *et al.* (1974). At a concentration of 100/100 ppm for $HCHO/HC\ell$, less than 0.1 ppb BCME (level of detection) was formed. Kallos and Solomon (1973) concluded that "occupational health problems would not be expected from hydrogen chloride and formaldehyde, since bis-chloromethyl ether is not formed even at concentrations of these reactants significantly above that which humans can tolerate" (TLV for $HCHO=2$ ppm; $HC\ell=5$ ppm).

Tou and Kallos (1974a) have considered the possibility that BCME might be formed in aqueous $HC\ell$ and formaldehyde mixtures. Because the hydrolysis rate of BCME in aqueous media is very rapid (half-life ~ 10-40 seconds - see Section I-B-2, p.11), it coult not exist in aqueous media for long periods of time. However, BCME formed in aqueous media might escape to the atmosphere where it is relatively stable (half-life greater than 25 hrs - see Section I-B-2, p.11). Tou and Kallos (1974a) used five solutions of equal concentrations of 1 to 1000 ppm of HCℓ and HCHO. They monitored both the aqueous solution and the air left in the reaction vessel. No BCME was detected in the aqueous media (limit of detection 9 ppb) or in the gas phase above the reaction mixture (limit of detection 1 ppb).

The studies by Frankel et al. (1974) and Kallos and Solomon (1973) leave unresolved the question of occupational hazard from BCME possibly in mixtures of formaldehyde and hydrogen chloride vapors at high concentrations (500-3000 ppm). However, at lower concentrations, the studies agree that BCME formation seems unlikely. The study by Kallos and Solomon (1973) would suggest that BCME is not formed in aqueous solutions containing low concentrations of hydrochloric acid and formaldehyde. However, Frankel et al. (1974) have monitored the vapors above formalin slurries of Friedel-Crafts chloride salts and detected varying concentrations from 210 ppb with $FeCl_3$ to 1500 ppb with $AlCl_3$. Marceleno et al. (1974) also found BCME in solutions containing $MgCl_2$ catalysts.

Solutions which have been used to prepare BCME include: hydrogen chloride and aqueous formaldehyde; hydrogen chloride and sulfuric acid solution of paraformaldehyde; paraformaldehyde in concentrated hydrochloric acid with chlorosulfonic acid; hydrogen chloride and hexamethylenetetramine; and phosphorus trichloride, zinc chloride, and papaformaldehyde (Frankel et al., 1974). Goodson (1974) noted that hexamethylenetetramine, a once widely used urinary antiseptic, might form BCME in the acid environment of the stomach. However, Harris (1974) pointed out that hexamethylenetetramine has been administered as 1% in drinking water to mice and rats for 60 and 104 weeks, respectively, with no evidence of carcinogenicity.

From the available information, it appears that whenever formaldehyde is used in the presence of ionic chloride compounds, BCME may be formed. Whether it is formed in a particular situation needs to be determined by monitoring. This approach has been used by NIOSH (Marceleno and Bierbaum, 1974; Marceleno et al., 1974a,b).

Formaldehyde is produced in about 6 billion lbs a year. Table 23 lists the various applications of formaldehyde.

Table 23. Applications of Formaldehyde
(Chemical Marketing Reporter, 1975)

Use	Percent
Urea-formaldehyde resins	25
Phenolic resins	21
Polyacetal	8
Pentaerythritol	7
Hexamine	5
Melamine-formaldehyde resins	3
Tetrahydrofuran	3
Acetylenics	3
Export	2
Other	23

Marceleno and Bierbaum (1974) have considered the possibility of BCME formation from formaldehyde use in: (1) the paper industry, (2) the textile industry, and (3) medical and scientific applications. In the paper industry, it was found by walk-through surveys that formaldehyde and hydrochloric acid were stored separately and, in most cases, used separately. When they are used together (formaldehyde treated fibers immersed in a solution treated with hydrochloric acid), a basic condition prevails. In evaluating the medical applications, Marceleno and Bierbaum (1974) monitored BCME in the vicinity where the following histological techniques were being performed: Hematoxylin and Eosin Stain; Colloidal Iron-Periodic Acid; Schiff-Bismark Brown Technique; and Snook's Reticulum Stain. No BCME was detected with a limit of detection of 0.1 ppb.

With a textile pilot plant using formaldehyde resins and magnesium chloride and zinc nitrate catalysts in the permanent press process, some samples contained BCME, but the results were inconclusive (Marceleno and Bierbaum, 1974). Further monitoring of two textile concerns, Springs Mills, Inc., and Burlington Industries, by Marceleno and coworkers (1974a,b), provided several samples containing low ppb concentrations of BCME (highest concentration 2.7 ppb). No BCME was found in the Springs Mills plant and this was attributed to a switch from high chloride containing catalysts prior to the survey. NIOSH through the Bendix Corporation, is continuing to monitor selected work environments for BCME (Nat. Inst. Occup. Safety and Health, 1974).

α-chloroethers may also be produced by direct chlorination. For example, the reaction of 2000 g of chloromethyl methyl ether and 1100 g of chlorine at 18-25° with stirring and ultraviolet irradiation for 7 hrs yielded 376 g Cl_2CHOCH_3, 1174 g $ClCH_2OCH_2C\ell$, and 36 g $Cl_2CHOCH_2C\ell$ (Rieche and Gross, 1958).

The possibility of this reaction taking place commercially or without irradiation is unknown, but considering the toxicity of the products, an investigation seems worthwhile.

Another inadvertent source of production of haloethers, which has been shown to be an environmental contamination source, is the commercial chlorohydrin process. This source of production for bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether has been considered in some detail in Section II-A, p. 25. This discussion will focus on environmental contamination from chlorohydrin processes in general.

There are three major groups of commercial chlorohydrins: ethylene chlorohydrin, propylene chlorohydrin, and glycerol chlorohydrins (Lichtenwalter and Riesser, 1964). The haloether is formed during the chlorohydrination reaction as depicted in Figure 12.

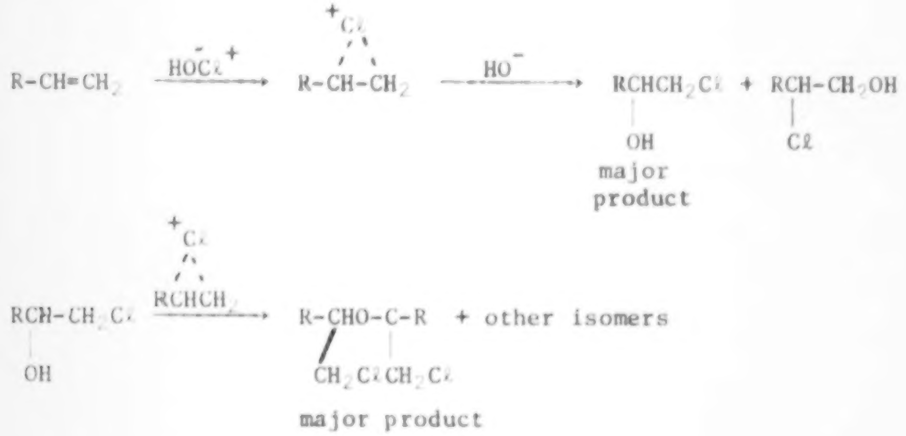
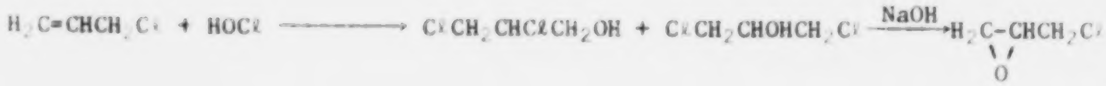


Figure 12. Formation of Chloroethers During Chlorohydrination (Lapkin, 1965; Schultze, 1965)

Formation of the chloroether during chlorohydrination has been demonstrated with ethylene chlorohydrin (Sherwood, 1949; Silov, 1945; Schultze, 1965) and propylene chlorohydrin (Lapkin, 1965; Blackford, 1973b). However, the ethylene chlorohydrin route to ethylene oxide is no longer used commercially (Blackford, 1973a). In fact, most ethylene chlorohydrin that is produced now is made by hydrochloric acid reaction with ethylene oxide, the latter being made by the direct oxidation route. On the other hand, 70% of the propylene oxide capacity (1275 million lbs) is still based upon the chlorohydrin process. Horsley (1968) estimates that a typical propylene chlorohydrin plant produces approximately 2 lbs of dichloropropyl ethers [three isomers - major one is bis(2-chloroisopropyl)ether] for every 100 lbs of propylene oxide, and this has been confirmed by Dow Chemical (Otis, 1975). Kleopfer and Fairless (1972) have detected 0.5 - 35 mg/ℓ of bis(2-chloroisopropyl)ether in an industrial outfall 150 river miles upstream from Evansville, Indiana (probably Olin propylene oxide plant at Brandenburg, Kentucky - annual capacity 130 million lbs). If one assumes a daily discharge of 150 lbs (Kleopfer and Fairless, 1972), production at 90% of capacity, and similar losses at other plants, an annual loss of approximately 47,000 lbs per 100 million lbs of propylene oxide produced by chlorohydrination is possible. In 1973, this could amount to a loss of 600,000 lbs. However, Dow Chemical indicated that they collect and burn most of their by-product bis(2-chloroisopropyl)ether, although they do emit about 20 lbs/day of bis(2-chloroisopropyl)ether in the air effluent from their chlorohydrin oxide plants (Otis, 1975). Whether this practice is used in other propylene chlorohydrin plants is unknown. Dow's water effluents contain 3-5 ppm bis(2-chloroisopropyl)ether before bioxidation treatment and no detectable chloroether after treatment. Bis(2-chloroisporpyl)ether has also been detected in an unspecified glycol plant's thickening and sedimentation pond (Webb *et al.*, 1973). Propylene glycol is made from propylene oxide.

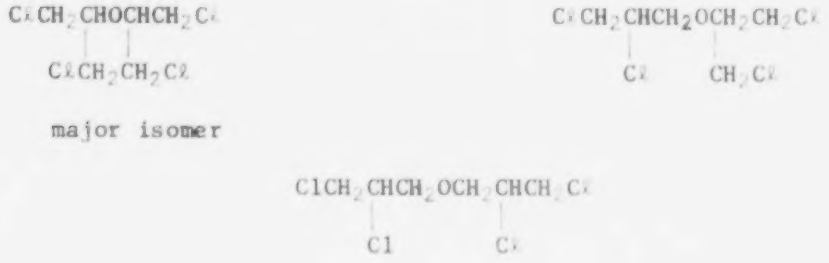
Another potential, but unconfirmed, source of chloroethers is the chlorohydrination route to epichlorohydrin. Epichlorohydrin is produced by chlorohydrination of allyl chloride followed by base cyclization to the epoxide (see Figure 13).



$$H_2C{=}CHCH_2Cl + HOCl \longrightarrow ClCH_2CHClCH_2OH + ClCH_2CHOHCH_2Cl \xrightarrow{NaOH} \underset{O}{H_2C\text{-}CH}CH_2Cl$$

Figure 13. Production of Epichlorohydrin by Allyl Chloride Route (Oosterhof, 1970)

Some of the crude epichlorohydrin is further hydrolyzed to synthetic glycerin, and the rest is refined by a two-column distillation in which some light and heavy ends are removed. The ethers that could be formed are similar to the propylene chlorohydrin ethers, except that they contain two extra chlorine atoms (see Figure 14). Because they are not α-chloroethers, they should be fairly stable in water. Table 24 lists the producers, capacities, and plant locations of epichlorohydrin manufacturers where these chloroethers might be formed.



$$ClCH_2\underset{ClCH_2}{CH}O\underset{CH_2Cl}{CH}CH_2Cl$$

major isomer

$$ClCH_2\underset{Cl}{CH}CH_2O\underset{CH_2Cl}{CH_2}CH_2Cl$$

$$ClCH_2\underset{Cl}{CH}CH_2OCH_2\underset{Cl}{CH}CH_2Cl$$

Figure 14. Potential Chloroethers From Epichlorohydrin Manufacture

Table 24. Producers of Epichlorohydrin (SRI, 1975)

Company	Location	Capacity (millions of lbs)
Dow Chemical	Freeport, TX	275
Shell Chem. Co.	Deer Park, TX	160
	Norco, LA	60
		495

7. Potential Inadvertent Production in the Environment

Recent contamination problems from halogenated hydrocarbons in drinking water (e.g., Dowty et al., 1975) have raised the question of the possible formation of chlorinated compounds in water due to chlorination. Chlorination of ethers in water at low concentrations has not been studied. However, the first chlorination step, if it occurs, is probably substitution of a chlorine atom on the α-position of the ether (Summers, 1955). Since α-chloroalkyl ethers hydrolyze very rapidly in water, the possibility of chloroethers being a drinking water contaminant seems fairly remote.

D. Current Handling Practices and Control Technology

Information in this category is very limited and applies mostly to BCME and CMME in the occupational environment. The available information is briefly reviewed below and in Section IV-A, p. 149) (Current Regulations).

1. Special Handling

Both BCME and CMME are regulated under Occupational Safety and Health Standards (OSHA, 1973; OSHA, 1974a,b). This requires that the materials be handled only in "closed system" operations where containment prevents the release of the chemical into regulated areas, non-regulated areas, or the external environment. Employees engaged in transfer operations must wear full-face, supplied-air respirators and full-body protective clothing.

With bis(2-chloroethyl)ether, Allen (1956) has suggested that workers be provided with activated charcoal respirator canisters where high concentrations are encountered.

2. Methods of Disposal and Storage

No information on recommended disposal methods was located in the available literature. However, the instability of BCME and CMME in water make it likely that water hydrolysis is used at least with these two compounds. Also, Dow Chemical states that they burn any bis(2-chloroisopropyl)ether that is formed as a by-product from their propylene chlorohydrin process (Otis, 1975).

3. Accident Procedures

When accidents occur with BCME and CMME, the affected area should be evacuated as soon as possible and the following actions undertaken: (1) the hazardous condition should be eliminated before resumption of normal procedures, (2) special medical surveys should be instituted, and (3) employees having contact with the chemical should shower as soon as possible (OSHA, 1974a,b).

4. Current Controls

Controls on the non-α-haloethers were not noted in the available literature. However, with the effluent from propylene oxide and glycol plants, Lapkin (1965) suggests that:

> "Plant location and local ordinance restrictions determine the method of disposal. Whenever local conditions permit, the effluent is simply discharged into a sufficiently large body of water flowing to the sea. In some cases, the effluent is treated by a sewerage works before it is directed to a water tributary."

Current controls for BCME and CMME have been preventive in nature. For example, the National Institute of Occupational Safety and Health (1974) has recommended that textile manufacturers change their processes to use resins low in free formaldehyde and substitute catalysts low in ionic chloride (e.g., use zinc nitrate instead of magnesium chloride). Also, they recommended that continuous ventilation be supplied in areas where formaldehyde and ionic chloride might come in contact.

E. Monitoring and Analysis

1. Analytical Methods

In the last several years, considerable research activity has been devoted to analytical methods development for non-anesthetic haloethers. This activity has been directed at techniques that are sensitive and specific for haloethers at ppb concentrations. However, the techniques that have been used with the anesthetic gases are not as sensitive or specific.

Kelley (1967) has reviewed the techniques available for fluroxene ($CF_3CH_2OCH=CH_2$) and methoxyflurane ($CHC\ell_2CF_2OCH_3$). Methoxyflurane can be determined by assaying for fluorine (not very sensitive). Volatile impurities in methoxyflurane can be determined by gas chromatography. Fluroxene can also be determined by fluorine assay, but a more sensitive technique (good to 1 mg of fluroxene/100 ml blood), devised by Linde (1956), consists of passing the blood distillate through a methanol solution containing a known amount of bromine. The bromine quantitatively reacts with the vinyl group and the amount of fluroxene is determined by titrating the remaining bromine with thiosulfate. Kelly (1967) also noted a direct injection gas chromatographic technique for analyzing 0-160 μg of fluroxene in 25 $\mu\ell$ of blood.

A number of techniques besides those noted above have also been used to determine methoxyflurane. For example, Chenoweth et al. (1962) used infrared spectrometry for the quantitation of methoxyflurane in blood, tissue, and exhaled air samples. The air samples were placed in a gas cell and concentrations down to 0.28% were determined. The blood and tissue samples were extracted with carbon disulfide before infrared quantitation, and the lowest concentration measured was 28 ppm by weight. Gelb and Steen (1969) have used a dielectric analysis technique to continuously monitor methoxyflurane in an oxygen-nitrous oxide stream. By measuring the capacity change which results from the difference in dielectric constants between the methoxyflurane gas and the oxygen-nitrous oxide gases, concentrations down to $3 \mu g/cm^3$ could be continuously detected.

Both Santo (1966) and Jones et al. (1972) have used gas chromatography for analysis of methoxyflurane in biological samples. Santo (1966) used C^{14}-labelled methoxyflurane and a gas radio-chromatographic system to determine tetrachloroethylene-extracted methoxyflurane in samples of blood, plasma, urine, spinal fluid, etc. The sensitivity of the technique is probably quite high, although it was not reported. However, the method does require the synthesis or purchase of radiolabelled compounds.

Jones et al. (1972) noted that a number of techniques including gas equilibration, distillation, and chemical extraction have been used to extract anesthetics from blood before analysis. The last technique has the advantage that it can be commenced as soon as the sample is taken, therefore, reducing the risk of leakage from the sample. However, most of the available volatile commercial solvents interfered with subsequent gas chromatographic analysis. Therefore, Jones and coworkers (1972) chose a non-volatile liquid (silicone fluid) that could be directly injected into a gas chromatograph after the extraction of methoxyflurane by equilibration. The technique provided linear response and good reproducibility at concentrations of 1-20 mg/100 mℓ of blood.

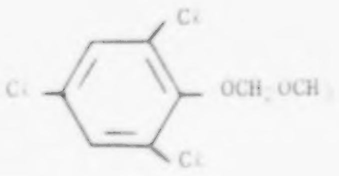
The discovery of the carcinogenic properties (see p. 86) of BCME has stimulated analytical development efforts at two major chemical companies; Rohm and Haas and Dow Chemical. The techniques were developed for measuring BCME or CMME at low concentrations in order to analyze air samples, as well as to determine the rate of formation (from formaldehyde and chloride ion) or hydrolysis of BCME. Collier (1972) devised a method for measuring BCME at the 0.1 ppb level in air samples. The technique consisted of adsorbing the compound on an aromatic copolymer in bead form (Porapak Q) followed by thermal elution directly into a mass spectrometer. The mass spectrometer is set to measure ions at m/e 78.9950 ($C\ell CH_2\text{-}O\text{-}CH_2^+$) with a resolation of 1/3500.

Shadoff and coworkers (1973) used the same trapping technique (Porapak Q), but selected gas chromatography-mass spectrometry (GC-MS) for analysis. The sensitivity was 1 Vppb (4.7 ng/ℓ of air). GC-MS analysis was selected in order to achieve three ways of specificity: (1) characteristic retention time on gas chromatography, (2) most intense ion at m/e 79 and 81 (loss of one chlorine atom from the molecular ion, and (3) the relative ratio of m/e 79 to 81 must be 3:1 due to the chlorine isotopic abundance. The authors felt that the added specificity of the gas chromatograph was required for monitoring BCME in air samples which contained large excesses of CMME (this is quite likely since BCME is an impurity in CMME). The mass spectrometry technique of Collier (1972) would have serious interference problems caused by the ion, $C\ell CH_2OCH_2^+$, which is found in the mass spectrum of CMME (m/e 79 is 0.14% of the major peak at m/e 45).

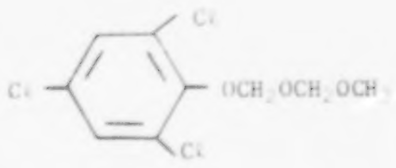
In order to obtain even more specificity and sensitivity, Evans and coworkers (1975) have combined gas chromatography with high resolution mass spectrometry. Monitoring the ion m/e 78.9950 ($C_2H_4OC\ell^+$) from BCME, they were able to measure down to levels of 0.1 ppb v/v BCME on a 1 ℓ air sample and 0.01 ppb v/v BCME with a 10 ℓ air sample. Poropak Q was used for pre-concentration.

Marceleno and coworkers (Marceleno and Bierbaum, 1974; Marceleno et al., 1974a,b) have used Poropak Q, Tenax, and Chromosorb 101 as absorbers in the analysis of BCME in occupational situations (textile plants and medical laboratories). Drying tubes were employed ahead of the Poropak Q samples in areas in the textile plants where excessive heat and moisture would hinder BCME uptake by the absorber. Considerable effort was expended to overcome tube in-line resistance so as to utilize portable low flow samplers. The samples were submitted to Rohm and Haas and to Dow Chemical for analysis.

Soloman and Kallos (1975) concluded that although GC-MS techniques were very specific and sensitive, they did not lead themselves to on-site plant monitoring because of the sophisticated equipment required. Therefore, they used a derivative approach with gas chromatography for detecting BCME or CMME at low ppb concentrations. The air sample being examined was drawn through two impingers containing a methanolic solution of the sodium salt of 2,4,6-trichlorophenol. The derivatives I and II were identified for CMME and BCME, respectively.



I



II

Because these derivatives are chlorinated aromatic compounds, they are well suited for detection by electron capture.

Kallos and Solomon (1973) used the GC-MS technique of Shadoff *et al.* (1973) to detect the possible formation of BCME in simulated hydrogen chloride-formaldehyde atmospheres. However, they used Chromosorb 101 rather than Poropak Q for adsorptive concentration. A detection limit of 0.1 ppb was reported when 15 liters of air were sampled.

Frankel *et al.* (1974) also studied the formation of BCME from formaldehyde and hydrogen chloride in moist air. They used three different analytic methods, all of which were sensitive to <0.5 ppb with 15 liters samples. Each method required a concentration step (Poropak Q). Quantitation was provided by: (1) high resolution mass spectrometry (Collier, 1972), (2) GC-MS [similar to Shadoff *et al.* (1973)], and (3) dual column chromatography. The dual column chromatographic system consisted of two temperature-programmed gas chromatographic columns connected in series. Connecting the columns was a valve that allowed the BCME fraction from the first column to be transferred to the second column. Quantitation was provided by a flame ionization detector.

Westover and coworkers (1974) have devised a rather novel method of direct sampling of volatile organics in both aqueous solution and air. Hollow fiber probes, usually constructed of silicone rubber, are placed directly into the medium to be analyzed and connected to a mass spectrometer. The probe provides the pressure reduction required by the mass spectrometer and also enriches the concentration of the material to be analyzed. In order to demonstrate the usefulness of hollow fiber probes in direct monitoring, Westover et al. (1974) embedded a probe in the venous blood stream of a rat. When the rat was exposed to methoxyflurane ($CHC\ell_2CF_2OCH_3$), response in the mass spectrometer was noted approximately 0.5 min. after the start of exposure and reached a maximum at 1.5 min.

Because the hollow fiber probe - mass spectrometry technique is capable of continuous analysis, it is the method of choice for kinetic studies. Tou et al. (1974) used the technique in order to determine aqueous hydrolysis rates of BCME under both basic and acidic conditions (see Figure 15 for the apparatus). The rate determinations were carried out at approximately 1 ppm. Tou and Kallos (1974a) used the method to study the possible formation of BCME in aqueous solutions of HCℓ and formaldehyde.

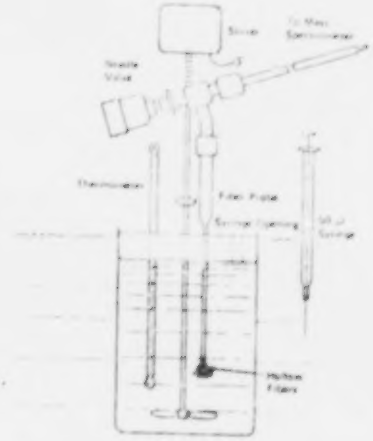


Figure 15. Bis(chloromethyl)ether Hydrolysis Apparatus
(Tou et al., 1974)
(Reprinted with permission from American Chemical Soceity)

They monitored both the aqueous phase and the gas phase above the reaction mixture (limits of detection were 9 ppb and 1 ppb, respectively). The same technique was also used by Tou and Kallos (1974b) to determine the stabilities of CMME and BCME in humid air.

The previously described analytical methods have all been used in clinical and laboratory studies or in occupational environments. They have not been used to analyze ambient air or water samples. However, haloethers have been detected in river water and municipal drinking water. The most frequently used technique for isolating the compounds is to filter large volumes of water with a carbon filter followed by extraction of the organics from the carbon by chloroform extraction (carbon chloroform extract, CCE). This isolation technique has been used for years, and haloethers have been detected as early as 1963 using the procedure (Rosen et al., 1963). Usually enough material is isolated to allow conventional identification techniques (e.g., infrared spectrometry) to be used. The carbon chloroform isolation technique has also been used in a number of recent studies (Friloux, 1971; Kleopfer and Fairless, 1972; and the U.S. Environmental Protection Agency, 1972, 1974). A disadvantage of the technique is that only qualitative concentrations can be reported when the efficiencies of the isolation process are not determined. For example, researchers examining water supplies in the New Orleans area (U.S. Environmental Protection Agency, 1974) reported their results in terms of "highest measured concentration." By knowing the quantity of water sampled and by assuming efficiencies for the isolation technique, a qualitative concentration can be estimated. However, in order to determine quantitative concentrations, "the efficiency of the carbon adsorption from water, losses incurred in carbon drying, efficiency of desorption by solvent from the carbon, and losses incurred in concentrating the solvent to a low volume" (U.S. Environmental Protection Agency, 1974) would have to be determined for each compound detected.

Besides using the CCE procedure, Kleopfer and Fairless (1972) also developed a direct extraction procedure for determining bis(2-chloroisopropyl)ether in tap and raw unfinished water. The procedure consisted of extraction with 5% ethyl ether in hexane, concentrating the solvent, and quantitation by gas chromatography with flame ionization and electron capture detection. The lowest concentration reported was 0.2 μg/ℓ (ppb).

2. Monitoring

The available information on monitoring of haloethers in water is difficult to assess due to a confusing use of nomenclature. Also, some of the compounds which have been reported have such a fast rate of hydrolysis (see Section I-B-2, p.11) that it would appear very improbably that they would be detected in raw or finished (drinking) water. The available information is summarized in Table 25.

The confusing nomenclature (e.g., is bis-chloroethyl ether the same as dichloroethyl ether) and instability of some of the compounds (e.g., chloromethyl ether and chloromethyl ethyl ether) raises questions about the reliability of the Friloux (1971) and U.S. Environmental Protection Agency (1972) data. However, the rest of the studies rather convincingly indicate that bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether are wide-spread water contaminants.

The major source of bis(2-chloroisopropyl)ether contamination, at least for the Evansville drinking water, appears to be an industrial outfall about 150 river miles upstream from the Evansville water intake. Kleopfer and Fairless (1972) detected concentrations of bis(2-chloroisopropyl)ether in the outfall ranging from 0.5-35 μg/ℓ (estimated discharge of 150 lbs/day). By assuming a discharge of 150 lb/day, a river flow of 50,000 ft^3/sec, no biodegradation, and perfect mixing, the authors calculated a concentration at Evansville of 1.8 μg/ℓ. In August-September 1971, the measured concentration in the Ohio River at Evansville ranged from 0.5-5 μg/ℓ. Above the industrial outfall, the concentration in the Ohio River was less than 0.2 μg/ℓ. From their experience with bis(2-chloroisopropyl)ether, Kleopfer and Fairless (1972) concluded that "the compounds [bis(2-chloroisopropyl)ether and bis(2-chloroethyl)ether] are by-products in the manufacturer of propylene glycol and ethylene glycol, respectively". Webb et al. (1973) have also detected bis(2-chloroisopropyl)ether in the thickening and sedimentation pond of a glycol plant.

Table 25 Haloethers Detected in Industrial Raw and Finished Waters

Reference	Compound	New Orleans Finished Water (general)	Louisville	[illegible]	[illegible]	Kanawha River, Nitro, W.V.	Philadelphia Drinking Treatment Plant	Delaware River - Philadelphia	Synthetic Rubber Plant's Treated Effluent	[illegible] Plant's [illegible]	Evansville Drinking water	Ohio River water at Evansville
Rosen et al. (1963)	bis(2-chloroethyl)ether					X						
Friloux (1971)	bromophenyl phenyl ether	X										
	chloroethyl ether	X										
	chloromethyl ethyl ether	X										
	dichloroethyl ether	X										
U.S. EPA (1972)	bromophenyl phenyl ether		X		X							
	bis-chloroethyl ether		X		X							
	chloromethyl ether		X									
	bis-chloroisopropyl ether				X							
	dichloroethyl ether		X									
Kleopfer and Fairless (1972)	bis(2-chloroethyl)ether										X	
	bis(2-chloroisopropyl) ether										[illegible]	[illegible]
U.S. EPA (1974)	bis(2-chloroethyl)ether		[illegible]* µg/l	[illegible]* µg/l	[illegible]* µg/l							
	bis(2-chloroisopropyl) ether		[illegible]* µg/l	[illegible]* µg/l	[illegible]* µg/l							
Webb et al. (1973)	bis(2-chloroethoxy)methane								[illegible] mg/l			
	bis(2-chloroethyl)ether								0.28 mg/l			
	bis(2-chloroisopropyl) ether									X		
Anon (1975)	bis(2-chloroethyl)ether						[illegible] µg/l	[illegible] µg/l				

*Highest measured concentration in carbon chloroform extract.

Kleopfer and Fairless (1972) also examined whether conventional drinking water treatment would remove bis(2-chloroisopropyl)ether. When the concentration in the raw intake water was 2.0 μg/ℓ, the concentration in the Evansville tap water was 0.8 μg/ℓ.

The earlier study of drinking water in the New Orleans area (U.S. EPA, 1972) also examined a number of industrial outflows going into the Mississippi River. No haloethers were detected, but it is unclear whether any of the plants examined were manufacturing glycols.

Some sizable concentrations of bis(2-chloroethoxy)methane (140 mg/ℓ) and bis(2-chloroethyl)ether (0.16 mg/ℓ) have been detected in treated waste from synthetic rubber plants (Webb et al., 1973). This is not unexpected for bis(2-chloroethoxy)methane, since it is used as the principle monomer of polysulfide rubbers.

Recently, bis(2-chloroethyl)ether has been detected in the effluent from Philadelphia's Northeast treatment plant (10 ppb) and in the city's Deleware River intake (0.4 - 0.5 ppb) (Anon., 1975). Rohm and Haas has admitted that it has been discharging up to 135 lbs/day into the city sewer system. The company, which uses bis(2-chloroethyl)ether as an intermediate in surfactant production, plans to make process alterations to eliminate the chemical from the plant effluent.

NIOSH (Marceleno and Bierbaum, 1974; Marceleno et al., 1974a,b) has monitored the air inside one pilot and two full-scale textile plants, all of which used formaldehyde (a source of BCME) (these studies are reviewed in more detail in Section II-C-7, p. 63). In a number of the samples taken, BCME was detected at very low concentrations (1-2 ppb). This included one stack sample of gases being emitted into the ambient air from a textile plant tenter frame.

III. Health and Environmental Effects

A. Environmental Effect

1. Persistence

a. Biological Degradation

Very little information is available in the literature concerning the environmental fate of haloethers. BCME is known to hydrolyze rapidly in water; subsequently, its breakdown by microorganisms has not received any attention. The only haloethers which have been studied to some extent are bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether, the reason probably being that both of these compounds have been recognized as surface water pollutants (Rosen et al., 1963; Kleopfer and Fairless, 1972).

Ludzack and Ettinger (1963) studied the breakdown of bis(2-chloroethyl)ether (21.1 mg/ℓ) to CO_2 in Ohio River water buffered to a pH of 7.2 and supplemented with settled sewage (1% by volume was added weekly to the test medium). The authors found extensive degradation of the chloroether after 25-30 days lag period; about 85% of the theoretical CO_2 was recovered after 65 days of incubation. Upon redosing the biodegradation test medium with the chemical, CO_2 evolution occurred at rates several fold higher than the first time (indicating the necessity for acclimation of microorganisms to the haloether). The investigators did not attempt to identify the form in which the remaining 15% carbon was present.

The reported CO_2 evolution data was determined by subtracting the CO_2 evolved in the river water control from the CO_2 evolved in the test sample containing the ether. In river water supplemented weekly by the addition of settled sewage, the control rates may be expected to be fairly high; this questions the reliability of the calculated value of CO_2 evolved from the haloether. Unfortunately, the amounts of CO_2 evolved in the control and in the test sample were not reported. The test was run at a temperature close to that of summer (22-26°C) and, therefore, persistence under winter conditions is not known (Ludzack and Ettinger, 1963).

The fate of bis(2-chloroisopropyl)ether in river water has been briefly studied by Kleopfer and Fairless (1972). These researchers incubated the chloroether in raw Ohio River water in the laboratory and found no degradation after 5 days. Since the incubation period was restricted to only 5 days, no definitive conclusions can be drawn concerning the biodegradability of this compound. A long acclimation period is sometimes required before degradation can occur, as noted by Ludzack and Ettinger (1963) with bis(2-chloroethyl)ether. For this reason, the possibility that the degradation of bis(2-chloroisopropyl)ether would have occurred upon prolonged incubation cannot be excluded. Also, since the concentration of chloroether used in the study was considerably higher (33 mg/ℓ) than the concentrations detected in the Ohio River water (0.5-5 μg/ℓ), a question can be raised about the possible inhibitory action of the test haloether on the microorganisms responsible for its degradation.

Bis(2-chloroisopropyl)ether does appear to biodegradate under activated sludge waste water treatment conditions. Dow Chemical reports that water effluents from their chlorohydrin oxide plants contain 3-5 ppm bis(2-chloroisopropyl)ether before bioxidative treatment and no detectable amounts (limit of detection unknown) after treatment (Otis, 1975).

Extrapolation of the laboratory results to the biodegradability of haloethers in nature is difficult. From the studies described above, it may be tempting to conclude that bis(2-chloroethyl)ether is extremely biodegradable, whereas bis(2-chloroisopropyl)ether is persistent. The widespread occurrence of these chemicals in the natural waters of the United States (see Section II-E-2, p. 72 on Monitoring) might suggest, however, that both bis(2-chloroisopropyl)ether and bis(2-chloroethyl)ether persist in the aquatic environment for extended periods of time. The monitoring data of Kleopfer and Fairless (1972) may help to resolve this question at least with bis(2-chloroisopropyl)ether. These researchers found that the concentration of bis(2-chloroisopropyl)ether in the industrial outfall located 150 miles upstream (on the Ohio River) from Evansville, Indiana, was in the range of 0.5-35 mg/ℓ. Assuming a discharge of 150 lb/day, a river flow of 50,000 ft^3/sec, no biodegradation, and perfect mixing, Kleopfer and Fairless (1972) calculated the expected concentration of the haloether at Evansville to be 1.8 μg/ℓ. The actual concentration found in the Ohio River at Evansville was 2.0 μg/ℓ in August, 1971 (concentration range 0.5-5 μg/ℓ, August-September, 1971). These findings suggest that bis(2-chloroisopropyl)ether remained relatively unaltered, at least during the time period required for transport of the haloether 150 river miles. Unfortunately, similar monitoring information is not available for bis(2-chloroethyl)ether, and, thus, no definitive conclusions can be drawn concerning its fate in the environment.

b. Chemical Degradation in the Environment

Information pertinent to determining the possibility of chemical degradation of haloethers is reviewed in Sections I-B-2, p. 11, and I-B-3, p. 21. From that information, it is apparent that α-haloethers will hydrolyze very rapidly ($t_{1/2}$<2 min), while the non-α-chloroethers hydrolyze very slowly. BCME would form hydrochloric acid and formaldehyde and CMME would degrade to hydrochloric acid, formaldehyde, and methanol. The chloroethers that are not susceptible to hydrolysis also appear to be relatively stable under photolytic and oxidative conditions.

2. Environmental Transport

No work has been reported concerning the transport of haloethers in the environment. However, some predictions can be made based on the physical properties of haloethers. The vapour pressure of a chemical determines to a great extent the possibility of the compound vaporizing into the atmosphere. The high vapour pressure of bis(2-chloroethyl)ether (0.73 mm Hg at 20°C; 1.6 mm Hg at 25°C; Hake and Rowe, 1963) and bis(2-chloroisopropyl)ether (0.71 - 0.85 mm Hg at 25°C; Hake and Rowe, 1963) suggests that these compounds are volatile enough to enter and distribute through the atmosphere. Mackay and Wolkoff (1973) have developed an approach to predict the rate of evaporation of compounds from water bodies to the atmosphere using the water solubility and vapor pressure of the compound. The equation for predicting residence time is based on the assumptions that the water column undergoes continuous mixing and that the compound is present in true solution and not adsorbed, complexed, etc. Using this approach, the calculated half-life for bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether at less than saturation concentrations in a square meter of water would be 5.78 days and 1.37 days, respectively (for comparison, DDT's half-life is 3.7 days, dieldrin's, 723 days).

In view of their appreciable water solubility (10.7 g/ℓ for bis(2-chloroethyl)ether, and 1.7 g/ℓ for bis(2-chloroisopropyl)ether, it appears likely that these ethers will be washed out of the atmosphere with rain. Thus, a continuous cycling of the haloethers between air and water is likely. Because of their high water solubility, the haloethers can also be expected to migrate through soil and eventually make their way to ground water.

The mobility of bis(2-chloroisopropyl)ether in the aquatic environment has been examined in an indirect way by Kleopfer and Fairless (1972). These investigators monitored the concentration of bis(2-chloroisopropyl)ether in the Ohio River 150 miles from an industrial outfall, and found that the pollutant was present at approximately the level calculated theoretically by taking into account the dilution factor (see Section III-A-1, p. 76). This suggests a fairly high mobility of bis(2-chloroisopropyl)ether in the aqueous environment and that appreciable loss of the haloether due to adsorption to hydrosoil, evaporation, or degradation does not occur during transport, at least over 150 river miles in the Ohio River.

In summary, although sufficient information is not available to allow any definite conclusions about environmental transport and distribution of haloethers, the physical properties indicate that bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether should be quite mobile in the environment.

3. Bioaccumulation and Biomagnification

No experimental data could be located in the literature concerning the bioaccumulation and biomagnification potential of haloethers. However, to some extent, it may be possible to predict their behavior from their physical and chemical properties. Accumulation of a chemical occurs when the chemical is taken into biological material and accumulated faster than it is eliminated. Kenaga (1972) suggested that the characteristics of a molecule which will affect its bioaccumulation potential will be solubility, partition coefficient, latent heat of solution, and polarity. However, if a compound is readily decomposed in the environment, it will be less likely to bioaccumulate. In assessing the bioaccumulation potential of the haloethers, their solubility, partition coefficient, and environmental persistence have been considered.

The available information on biodegradability, although it does not allow any definite conclusions, suggests that haloethers, such as bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether, are not rapidly attacked by microorganisms, and, therefore, may be expected to come in contact with food chain organisms. On the other hand, the α-chloroethers (e.g., BCME and CMME) hydrolyze rapidly in water (see Section I-B-2, p.11) and, therefore, are not likely to be around to be taken up by organisms. Thus, it seems highly unlikely that BCME or CMME would bioaccumulate.

The partition coefficient (ratio of the equilibrium concentration of the chemical between polar and non-polar solvent) has been used in assessing a chemical's bioconcentration potential. Neely _et_ _al_. (1974) have reported a linear relationship between octanol-water partition coefficients and bioconcentration of chemicals in trout muscle. Using the equation of the straight line of best fit, derived by Neely _et_ _al_. (1974), the bioconcentration factor of diethyl ether (octanol-water partition coefficient, 25°C = 5.9, Leo et al., 1971) is calculated to be approximately 3.5. Since the substitution of chlorines on ether tends to reduce its water solubility (e.g., the solubility of bis(2-chloroethyl)ether in water is one-sixth that of ethyl ether) and increase the lipid solubility, the bioconcentration factor for bis(2-chloroethyl)ether will probably be somewhat higher.

Biomagnification refers to concentration of a compound through the consumption of lower organisms by higher food chain organisms with a net increase in tissue concentration (Isensee et al., 1973). The biomagnification potential of haloethers has not been studied. To some extent, the water solubility of haloethers may be helpful in predicting their biomagnification potential. Metcalf and Lu (1973) have found that ecological magnification of several chemicals (concentration in organisms/concentration in water) in their model aquatic ecosystem follows a straight line relationship with water solubility. Using this relationship, the ecological magnification for bis(2-chloroethyl)ether and bis 2-(chloroisopropyl)ether is calculated to be approximately 1 and 5, respectively (for comparison, DDT is approximately 17000). From this calculation, it appears that the haloethers, bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether will not biomagnify to a significant extent in the food chain organisms.

B. Biology

Specific information on the absorption, distribution, metabolism, and elimination of the chloroethers is not available in the published literature. Unpublished sources of this information or current research in this area have not been encountered.

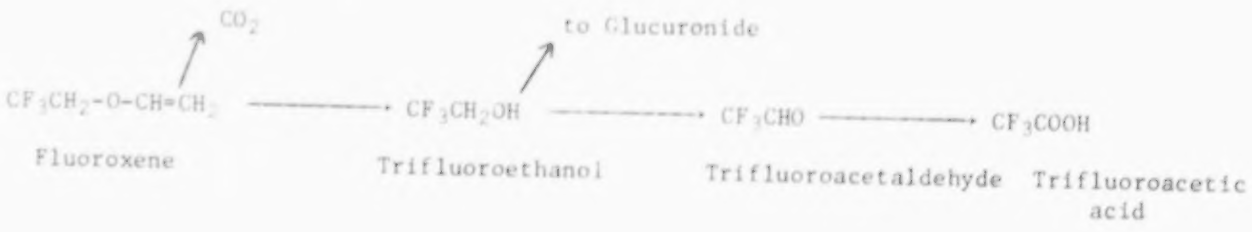
For the α-chloroethers, BCME and CMME, this is neither surprising nor particularly disturbing. These α-haloethers, as previously discussed, are powerful alkylating agents and are subject to rapid hydrolysis. Thus, by environmentally feasible routes of entry - i.e. oral, dermal, or inhalation - these agents would either hydrolyze to simple organic compounds and hydrochloric acid or be alkylated by any number of reactive sites in the biological material. As a result, they would not be expected to undergo biological transport and modification in the usual sense. At the cellular level, these compounds are stable enough to interact with receptor sites and cause cancer. This aspect of α-chloroether biology is discussed in detail below (see Section III-D-6, p. 126). In addition, one study indicates that BCME is stable enough to be injected subcutaneously into the middorsal area of mice and cause lung tumors (Gargus et al., 1969). Nevertheless, these compounds are so unstable that their residence time in the body is probably extremely short.

The same cannot be said for the β-chloroethers. These compounds are much more chemically stable and may be expected to be absorbed, transported, and metabolized to a significant extent. The lack of data in this area will be referred to repeatedly in discussing the known or potential toxic effects of these compounds.

The biological behavior of other ethers is, of course, relatively well characterized. Most notable, in this respect, are the anesthetics diethyl ether, fluroxene (2,2,2-trifluoroethoxy ethene), and methoxyflurane (2,2-dichloro-1,1-difluoro-methoxy ethane). Any attempt to extrapolate in detail the pharmacological characteristics of the β-chloroethers based on the behavior of these anesthetics would be tenuous at best. Nevertheless, some basic patterns are evident in the anesthetics, at least in their metabolism, which could conceivably apply to the β-chloroethers.

First, the ether bond can be cleaved by drug metabolizing enzymes. In mice exposed to diethyl ether, the ether bond is cleaved forming acetaldehyde and ethanol which are subsequently metabolized to carbon dioxide (Geddes, 1971). Cascorbi and Singh-Amaranath (1973) have recently shown that mice also cleave the ether linkage in fluroxene. The pathway which they propose for fluroxene biotransformation is given in Figure 16.

Figure 16. Postulated Pathway of Fluroxene Metabolism in Mice (Cascorbi and Singh-Amaranath, 1973)



Secondly, both defluorination and dechlorination have been demonstrated in the metabolism of methoxyflurane. Based on *in vitro* studies of human and rat liver microsomes, VanDyke and Wood (1973) have postulated the pathway shown in Figure 17 for methoxyflurane involving both ether cleavage and dehalogenation.

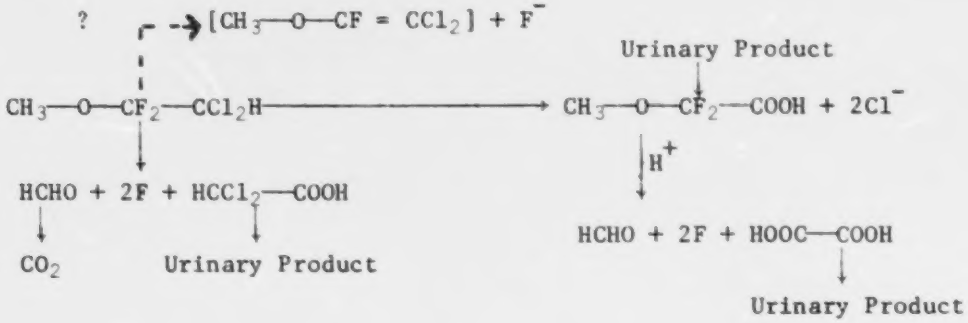


Figure 17. Proposed Pathway for the Metabolism of Methoxyflurane Based on Studies of Human and Rat Liver Microsomes (VanDyke and Wood, 1973)

In vivo studies with humans are consistent with this proposed pathway (Holaday *et al.*, 1970).

None of this, of course, has any definite relevance to the β-chloroethers. However, it does suggest, based on structural similarities, that the β-chloroethers may be subject to metabolic degradation. Given the complete absence of hard data, further speculation does not seem indicated. The potential relevance of the toxic effects of the fluorinated ethers to those of the chloroethers is discussed below (see Section III-D-1-d, p. 104).

C. Toxicity - Humans

1. Epidemiology

The consequences of occupational exposure to BCME and CMME have been examined in several recent epidemiological studies. The results clearly indicate that workers exposed to these chemicals have a markedly increased risk of developing respiratory cancer. Most studies indicate that one specific type of cancer, oal cell carcinoma, is prevalent. However, all of these studies are limited in two respects. First, quantitative levels of haloether exposure are not available. As indicated previously (see Section II-E, p. 65), reliable methods for monitoring these chemicals have only recently been developed and were generally not available to the epidemiologists involved in these investigations. Secondly, occupational exposure to CMME cannot occur without presuming simultaneous exposure to BCME, which is a contaminant (1-8%) in the synthesis of CMME. Consequently, in the following discussion, the term "chloromethyl ethers" is used to describe exposure to both BCME and CMME. The reverse, however is not the case. Exposure to BCME may occur without exposure to the monochloro analogue.

The initial indication that BCME caused cancer in man appeared in the literature in 1972. This report discussed the deaths of four male workers, ages 32 to 48, involved in the production of ion exchange resins using the chemical intermediate, CMME, with BCME being a minor contaminant in the CMME. All four deaths were due to lung cancer, with the youngest worker having been employed for only two years. Of the 100 workers in this plant (Diamond Shamrock Co., Redwood City, California), two more males subsequently developed lung cancer (Anon., 1972).

These findings prompted a more extensive study at this plant by Lemen and coworkers (1975) using both sputum cytology and retrospective analysis of the incidence of lung cancer in exposed workers. Sputum samples were obtained from both production workers exposed to the chloromethyl ethers and from office workers with no record of exposure. These samples were examined for atypia as an early indicator of bronchial epithelial damage caused by carcinogens.

When compared to the results of a similar survey of age-sex cigarette matched uranium surface employees as a negative control group, workers involved in the production of the chloromethyl ethers for more than five years showed a significant ($p<0.025$) increase in moderate and marked atypia. Workers exposed for less than five years and office employees with no record of haloether exposure had no significant increase in atypia.

Similar results were obtained in the retrospective analysis of lung cancer incidence. Using data on white Connecticut males between 1960 and 1962 to estimate an expected incidence of respiratory cancer, workers with probable exposure to the chloromethyl ethers for five or more years had an incidence of lung cancer more than nine times greater than expected (5/0.54, $p<0.01$). Four of the five cancers consisted of oat cell carcinomas. The mean exposure period for these cancer cases was 10 years with a mean induction - latent period of 15 years (Lemen _et al_., 1975).

Figueroa and coworkers (1973) published the first detailed report implicating BCME and CMME as human carcinogens. This study involved employees of the Rohm and Haas Co. chemical plant in Philadelphia, producing the chloromethyl ethers, and included both prospective and retrospective investigations.

In the prospective study, a group of 111 workers potentially exposed to the chloromethyl ethers were observed over a five year period. During this time, four men developed oat cell carcinoma of the lung (cases 4-7, in Table 26). Because all four of these men were in the age range of 35 to 54 - which comprised 88 of the 111 men in the study group - the five year lung cancer incidence was calculated as 4/88 or 4.54%. An expected incidence of lung cancer from a group not exposed to haloethers was based on data from the Philadelphia Pulmonary Neoplasm Research Project, which included 2804 men, ages 45 to 54, with smoking habits similar to the haloether exposed workers. This group had a five year lung cancer incidence of 0.57%. Thus, Figueroa and coworkers (1973) concluded that the risk of lung cancer development was about eight-fold greater in the chloromethyl ether exposed groups (4.54/0.57 or 7.96, $p<0.0017$).

This part of the study has been criticized for not including all 111 workers on the calculation of cancer incidence and for having a control group that underestimates the actual degree of risk involved. Brown and Selvin (1973), in correcting for these supposed errors, indicate that the actual increased risk due to haloether exposure may have been underestimated by a factor of 5.5, bringing the actual relative risk to 44.39. Although the original investigators disagree with the above criticisms, they do agree that the eight-fold increase in relative risk may be an underestimate, but for different reasons. First, the exact number of men examined in the prospective study who were actually exposed to haloethers could not be determined. Thus, the number of men at risk may have been overestimated. Secondly, oat cell carcinoma, which appeared in all four of the haloether exposed workers who developed cancer, comprised only 10% of the cancers in the control group (Weiss and Figueroa, 1973).

In the retrospective investigation, Figueroa and coworkers (1973) examined the available information on fourteen cases of lung cancer diagnosed in workers from the same plant. This information is summarized in Table 26.

Table 26. Lung Cancer in Workers Exposed to Chloromethyl Methyl Ether and Bis(chloromethyl)ether (Figueroa et al., 1973)

Case No.	Age yr.	Smoking History*	Duration of Exposure yr.	Date of Diagnosis	Histologic Type	Survival mo.
1	37	None	7	1962	Unknown	Unknown
2	33	1ppd/20	8	1962	Oat cell	7
3	39	1ppd/20	8	1962	Oat cell	6
4	47	1ppd/20	10	1963	Oat cell	18
5	52	1ppd/10	4	1964	Oat cell	11
6	47	1ppd/21	3	1964	Oat cell	8
7	43	1ppd/20	14	1966	Oat cell	4
8	53	2ppd/20	10	1969	Oat cell	4
9	48	1ppd/33	5	1970	Oat cell	11
10	50	1ppd/30	1?†	1970	Squamous	24
11	55	1ppd/40	12	1970	Oat cell	4
12	43	Pipe only	12	1970	Oat cell	20
13	37	None	14	1971	Oat cell	5
14	44	None	12	1971	Oat cell	10

*Packages/day (ppd) smoked/no. of yr.   †1 mo. according to fellow worker

*Estimates of exposure based solely on the memory of Case 14.

The prevalence of oat cell carcinoma in this group is particularly striking in view of its limited incidence (10% of respiratory cancers) in the control population.

Albert and coworkers (1975) have recently completed a similar retrospective survey of mortality data from 1948 to 1972 on workers in six firms producing the chloromethyl ethers. Causes of death were determined for about 1800 workers exposed for five or more years, and 8000 non-exposed workers (controls). The types of respiratory cancers found, however, are not specified. Between the two groups, yearly death rates did not vary significantly with the exception of deaths due to respiratory tract cancer. Here, age-adjusted yearly death rates were 1.48 per thousand for the exposed workers and 0.59 per thousand for the non-exposed workers. This represents an increased relative risk adjusted for age of 2.53 in the haloether exposed workers.

More detailed information is presented for one of the production plants studied, designated "Firm-one" by Albert and coworkers (1973). The probability of death due to respiratory cancer as a function of age is illustrated in Figure 18 for three groups: (1) workers in Firm-one exposed to the chloromethyl ethers for more than five years (2) non-exposed workers from Firm-one, and (3) Unites States white males between 1950 and 1967 [data for U.S. white males taken from Burbank, 1971].

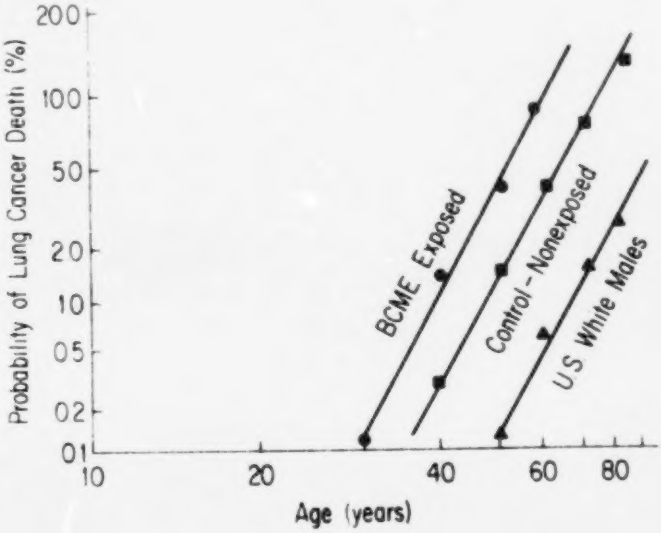


Figure 18. Cumulative Mortality - Corrected Probabilities of Lung Cancer Death in Bis(chloromethyl)ether [BCME] Exposed and Non-exposed Workers (Albert et al., 1975) Permission granted by author.

Comparing the data on the chloromethyl ether exposed and non-exposed workers in Figure 18, it is evident that comparable rates of death due to lung cancer occurred at a 15-20% earlier age in exposed workers, and at any given age exposed workers experienced a 3-4 fold increase in the rate of lung cancer death (Albert et al., 1975).

For workers in Firm-one, additional qualitative estimates were made of the relative intensities of maximum exposure to chloromethyl ethers - based on the type of job held by the worker - and the total duration of such exposure. Intensities of maximum exposure were then classified as low, medium or heavy. All 19 cases of lung cancer from this plant occurred in the heavy exposure group. [Since the report by Albert et al. (1975) has been drafted, the number of cases has increased to 25 (Shore, 1975).] Details for this group are presented in Table 27.

Table 27. Respiratory Cancer Deaths Among the Heavy Exposure Group Workers Exposed to "Chloromethyl Ethers" in Firm-one by Duration of Maximum Exposure (modified from Albert et al., 1975)

Total Duration of Maximum Exposure (years)	Years Elapsed Since First Exposure				Total* for 5 Elapsed Years	Age-Adj. Rate/1000/ Year**
	0-4 years	5-9 years	10-14 years	15-25 years		
≥5	0	1/1*	1/1	1/10	3/12	23.0
1-5	0	2/3	4/15	6/73	12/91	8.7
<1	0	0/8	0/27	4/153	4/188	1.5

* Number of deaths due to respiratory cancer/number of workers exposed

** Adjusted to the total exposed group in Firm-One. The control group had an adjusted rate of 0.97/1000/yr.

The increase in lung cancer death rate with increased duration of maximum exposure clearly suggests a causative role for these chloromethyl ethers as human respiratory carcinogens. For workers subject to heavy exposure for over five years, the relative risk of lung cancer death was increased by a factor of 23.7 (23/0.97) over the control population. Noting the increased latent period (15-20 years) seen in those heavily exposed workers with a total exposure period of under one year, Albert and coworkers (1975) indicate that the lack of abnormally high rates of respiratory cancer in the low and medium exposure groups may be due to an inverse relationship between dose and length of latent period.

Dow Chemical has recently furnished a report (Holder, 1973) on the cancer incidence in workers exposed to CMME and BCME. The degree of exposure was estimated only in total number of years worked in the exposure area. Age-specific mortality rates of a group of Dow Midland hourly employees (control) were used to estimate the number of expected deaths. Of the 104 men considered at risk, two deaths occurred from malignant neoplasms. One death involved a squamous cell carcinoma of the left lung which appeared 19 years after the beginning of a three year exposure period. The primary site of the other cancer case was not identified and death was attributed to generalized carcinomatosis. This occurred in an individual with seven years exposure who died fourteen years after exposure began. Based on the expected number of deaths from the control group, those exposed to the chloromethyl ethers for over one year with less than fifteen years since the first exposure have a 3.3-fold increase in total number of malignancies (1 observed/0.3 expected), but no increase in respiratory malignancies (0 observed/0.1 expected). Those exposed for over one year with more than fifteen years since the first exposure have a 10-fold increase in total malignancies (1 observed/0.1 expected) and an apparantly significant increase in respiratory malignancies (1 observed/0 expected).

Further, though, less detailed reports implicating the chloromethyl ethers as human carcinogens come from Germany (Thiess *et al.*, 1973) and Japan (Sakabe, 1973). In Germany, six of eighteen employees of a research institute, and two of fifty employees in a production plant all involved in the handling of BCME, died of lung cancer. Available details of exposure are summarized in Table 28 for the eight cases.

Table 28. Death from Lung Cancer in German Workers Associated with Bis(chloromethyl)ether Exposure (adapted from Thiess *et al.*, 1973)

Case No.	Period of Exposure (yrs)	Latent Period to Cancer Development (yrs)	Age at Death	Smoking Habits
1	6	8	59	+
2	6	10	53	+
3*	8	8	31	++
4*	9	9	52	?
5	6	15	65	+
6	6	16	42	None
7	6	16	58	+
8	6	16	60	+

*Employees at production facility. All others employed at research institute.

Of the eight cases of lung cancer cited, five were oat cell carcinomas. This is similar to the preponderence of oat cell carcinoma associated with chloromethyl ether exposure found by American investigators (Archer et al., 1975, and Figueroa et al., 1973). That these lung cancers may have been caused by exposure to very low concentrations of BCME is indicated by the fact that the production facility presumably utilized elaborate worker-production measures involving protective clothing, whole head fresh air masks, and exhaust equipment (Thiess et al., 1973).

Sakabe (1973) presents similar data on five cases of lung cancer which developed in a Japanesse dyestuff factory in which 32 employees were exposed to BCME between 1955 and 1971. Although the employees were exposed to over thirty different chemicals, BCME was assumed to be the most probable causative agent because of its known carcinogenicity in other mammals. Relevant details of these five cases are presented in Table 29.

Table 29. Deaths from Respiratory Cancer in Japanese Workers Associated with Bis(chloromethyl)ether Exposure (data from Sakabe, 1973).

Case No.	Total Duration of Exposure (years)	Time to Death After Initiation of Exposure (years)	Age at Death (years)	Estimate of Smoking Habits	Type Cancer
1	4	8.5	47	Moderate	Simple carcinomas of bronchia
2	5	12	38	Moderate	Oat cell cancer of bronchia
3	9	12.5	41	Moderate	Pancoast lung cancer
4	5	8	38	Heavy	Lung cancer (type not determined)
5	4	13	45	Moderate	Anaplastic adenocarcinoma papillotubulare

Based on the death rate due to respiratory cancer for the general population in Japan, the expected respiratory cancer mortality for a group of 32 people over the period in question was calculated to be 0.024. The five cases in this group of 32 workers thus amount to increased relative risk of 20.8[$p<0.001$] (Sakabe, 1973). It might be well argued that this study does not clearly implicate BCME as the causative agent in these cases of respiratory cancer. First, the workers were exposed to a variety of other chemicals (e.g., nitrobenzene and nitrophthalimide), which may have contributed to the development of respiratory cancer. Second, no estimates can be made of the degree of exposure to chloromethyl ethers. Lastly, oat cell cancer appeared in only one of the five cases. However, in view of the other epidemiological studies presented above and the detailed information on the carcinogenic effects of BCME on other mammals (see Section III-D-6, p. 126), such criticisms would be academic.

A summary of some of the more salient points in the epidemiological surveys discussed above is provided in Table 30.

Including the six most recent deaths reported by Shore (1975), a total of 47 deaths due to respiratory cancer have been associated with occupational exposure to the chloromethyl ethers. The increased risk of respiratory cancer deaths in exposed workers varies from about 2.5 to over 20. Albert and coworkers (1975) have demonstrated that this risk is dose-related to both the intensity and duration of exposure. The type of cancer associated with these exposures seems relatively specific, respiratory oat cell carcinomas. In view of all the epidemiological findings and the supportive laboratory data discussed

Table 30. A Comparison of Epidemiological Studies Associating Bis(chloromethyl)ether and/or Chloromethyl Methyl Ether with Respiratory Cancer [see text for details]

Reference	Number of Respiratory Cancer Deaths	Population at Risk	X Incidence or Rate of Cancer in Risk Group	Y Incidence or Rate of Cancer in Control Group	Increased Risk (X/Y)	Statistical Significance	Predominant Type of Cancer
Lemen *et al* 1975	5	136	5/1000/yr	0.54/1000/yr	7.4	p<0.01	Oat cell
Figueroa *et al.*, 1973							
Prospective Study	4	88	4.54/100/5 yrs	0.57/100/5 yrs	7.96	p<0.0017	Oat cell
Retrospective Study	14	-	-	-	-	-	Oat cell
Albert *et al.*, 1975							
Total Study	22	1800	1.48/1000/yr	0.59/1000/yr	2.53	-	Not specified
Heavy Exposure Group 5 yrs	3	12	23/1000/yr	0.97/1000/yr	23.7	-	Not specified
Thiess *et al.*, 1973	8	68	-	-	-	-	Oat cell
Sakabe, 1973	5	32	5/32/16 yrs	0.024/32/16 yrs	20.8	p<0.001	No predominant type

below, there can be no serious doubt that BCME is a potent human carcinogen. Lassiter (1973) has described it as possibly "one of the most potentially hazardous carcinogens found in the workplace". More recent data lend support to this assessment.

2. Occupational Exposure

Besides the rather extensive epidemological surveys discussed above, few cases of occupational injury resulting from exposure to the chloroethers are encountered in the literature. All the reported cases give little detail, but do cite or imply chemical irritation to the respiratory tract as the primary toxic effect. This is consistent with the known toxicity of these compounds in acute exposures to other mammals (see Section III-D-1, p.100). The available information on human occupational exposures is summarized below by chemical.

CMME: A report by Dow Chemical (no date) indicates that two workers were exposed to higher than normal concentrations of this α-haloether for a presumably short period. One worker was exposed to "rather high concentrations" while the other "received only very slight exposure". Both workers experienced respiratory difficulty. The most severely exposed individual could not work for eight days because of sore throat, fever, and chills. The other worker "had difficulty in breathing for several days".

1,2-Dichloroethyl ethyl ether: Jordi (1948a) describes three cases of bronchial asthma induced in workers after repeated exposures to "rather high" concentrations of this haloether. Initially, the workers developed headaches followed by irritation of the eyes and throat, and a painful cough. These symptoms disappeared during weekends and vacation periods. After several months of this exposure, all three workers developed severe bronchitis which was relieved by a stay in a sanitorium. On return to work, all three patients experienced attacks of bronchial asthma. In one worker, these attacks were experimentally induced by direct exposure to 1,2-dichloroethyl ethyl ether. A more severe attack was induced by an unspecified methyl derivative while bis-(2-chloroethyl)ether had no effect. The major toxic effects seemed limited to the respiratory tract with liver function being uneffected.

Bis(1-chloroethyl) ether: In anpther report, Jordi (1948b) also states that this α-haloether does not cause bronchial asthma but "has only a general toxic effect." No details are given.

Bis(2-chloroethyl) ether: This β-chloroether is generally regarded as less toxic than the α-chloroethers, but the type of overt hazard posed by vapor exposure is the same, chemical irritation of the respiratory tract and the eyes (Allen, 1956; Hake and Rowe, 1963). This assessment is based primarily on the work of Schrenk and coworkers (1933) which is summarized in the following section. Bell and Jones (1958) report than an occupational exposure to 2.5 ppm bis(2-chloroethyl)ether and unspecified amounts of chlordane and kerosene caused minor eye irritation. This chloroether may also have been a factor in the death of a worker exposed to an unspecified concentration of vapor from a solution containing bis(2-chloroethyl)ether. However, conclusive evidence indicating that this haloether was the cause of death is not presented (Elkins, 1959).

3. Controlled Human Exposures

In an evaluation of potential occupational hazard, Schrenk and coworkers (1933) have briefly exposed males to various concentrations of bis(2-chloroethyl)ether. Concentrations of 1000 ppm and 550 ppm were considered intolerable and caused extreme irritation of eyes and nasal passages. Deep inhalations caused nausea. Similar but less severe effects were caused at 260 ppm. This concentration was unpleasant but not intolerable. A concentration of 100 ppm caused only slight irritation and nausea. At 35 ppm, irritation was negligible, but the haloether was readily detected by its odor. Post-exposure respiratory difficulty was not noted.

4. Chemical Warfare Agents

Bis(2-chloroethyl)ether is the oxygen analog of Mustard Gas, 2,2' dichloroethyl sulfide. Both this latter chemical and its nitrogen analog are severe respiratory and dermal irritants (Allen, 1956; Jordi, 1948). The oxygen ether is, of course, much less reactive than either the nitrogen or sulfur analog and has never been developed as a chemical warfare gas. Norris (1919), however, reports that BCME was produced as a potential warfare agent during World War I. While this chemical was apparently never used in the war, Flurry and Zamik (1931) indicate that 3 ppm is very irritating to humans, and that 100 ppm is incapacitating in a few seconds and may cause fatal lung damage in one or two minutes.

D. Toxicity - Birds and Mammals

1. Acute Toxicity

a. Acute Oral Toxicity

Most of the information on the acute oral toxicity of the haloethers comes from the range finding studies of Smyth, Carpenter, and coworkers. These tests involve administering, by intubation, four dose levels of a compound to different groups of five to six unfasted animals. Mortality in the test animals is noted for fourteen days after exposure. Approximate LD_{50}'s are calculated either graphically or by interpolation (Smyth *et al.*, 1949). No pathological data are obtained, and no responses other than death are noted. Thus these tests are neither designed nor intended to give a reliable estimate of potential toxicity. Rather, they are used to estimate comparative hazard and "...yield no more than an indication of the degree of care necessary ..." in exposure to humans (Smyth *et al.*, 1969).

The available data on chloroethers are summarized in Table 31. The sources cited other than Smyth and Carpenter give few experimental details but would appear to pose limitations similar to those discussed above. Given the sparsity of detail and the few species tested, the differences in lethal dosages do not seem appreciable with one possible exception, bis(2-chloroethyl)ether. The LD_{50} values for this compound presented by Spector (1956) for rats, mice, and rabbits are somewhat lower than those for the other haloethers, and the value given by Smyth and Carpenter (1948) is well below. The significance of this observation, however, is dubious -- especially in view of the complete lack of information on metabolism.

Table 31. Acute Oral Toxicity of Various Haloethers

Compound	Organism*	mg/kg Dose(±1.96 S.D.)	Response	Reference
Bis(chloromethyl)ether	Rats, Male,(5), Carworth-Wistar, 4-5 weeks, 90-120 g.	300(172-530)	LD_{50} in 14 day observation period	Smyth *et al.*, 1969[+]
Chloromethyl Methyl Ether	Rats	300	No death	Dow Chemical, no date
		500	Approximate LD_{50}	
		1000	Lethal	
Bis(2-chloroethyl)ether	Rats, (6), Sherman	75	LD_{50}	Smyth and Carpenter, 1948[#]
	Rat	105	LD_{50}	Spector, 1956
	Mouse	136	LD_{50}	
	Rabbit	126	LD_{50}	
Bis(2-chloroisopropyl)-Ether	Rats, (6)	240(220-270)	LD_{50}	Smyth *et al.*, 1951
	Rats, (5)	200	No death	Dow Chemical, no date
	(6)	400	4/6 rats died	
	(5)	800	5/5 rats died	
	Guinea Pigs	450	LD_{50}	Spector, 1956
2-chloroethyl vinyl Ether	Rats, (6), Sherman	250	LD_{50}	Smyth *et al.*, 1949
Bis(2-chloroethoxy)-methane	Rat, Male, (5), Carworth-Wistar, 4-5 weeks, 90-120 g.	310(240-400)	LD_{50}	Smyth *et al.*, 1969

* The following data is included when given in reference:
Animal, Sex, (Number),
Strain
Age, Weight

[+] Cited as chloromethyl ether

[#] Cited as dichloroethyl ether

b. Acute Dermal Toxicity

Two types of dermal toxicity tests have been conducted with the haloethers: One measures lethal response and the other determines primary skin damage. The results of the studies measuring lethal response are given in Table 32. These studies are similar both in design and limitations to the acute oral administrations. In the work of Smyth, Carpenter, and coworkers, the test chemical is held in contact with the shaven skin of an immobilized animal for twenty-four hours either by cuff or poultice. Smyth and Carpenter (1948) indicate that the exposures using the poultice may prevent complete contact of the dose with the skin because much of the dose is absorbed by the saturated pad. In any event, because detailed information on time to death or blood levels is not given, the relative importance of rate of absorption as opposed to potency cannot be assessed. All that can be concluded with confidence is that lethal amounts of the specified chloroethers may penetrate the skin.

Table 32. Acute Dermal Toxicity of Haloethers

Compound	Organism	#Dose, mg/kg (±1.96 S.D.)	Response	Reference
Bis(chloromethyl)ether	Rabbit, Male, (4) New Zealand albino 2.5 - 3.5 kg	400(190-890)	LD_{50} in 14 day observation period	Smyth et al., 1969*
Bis(2-chloroethyl)ether	Guinea Pig	366	LD_{50} in 14 day observation period	Smith and Carpenter, 1948**
	Rabbits	90(55-145)Δ [as 10% sol. in propylene glucol.]	LD_{50} after 24 hr. exposure	Dow Chemical, no date
	Rabbits	100% solution, does not specified	Lethal amounts rapidly penetrated skin and caused death in one day	Dow Chemical, no date
Bis(2-chloroisopropyl)-ether	Rabbit	334(198-560)	LD_{50} in 14 day observation period	Smyth et al., 1951*
2-Chloroethyl vinyl ether	Rabbit	3.2 ml/kg	LD_{50} in 14 day observation period	Smyth et al., 1949*
Bis(2-chloroethoxy)methane	Rabbit, Male, (4), New Zealand albino, 2,4 - 3.5 kg	290(304-436)	LD_{50} in 14 day observation period	Smyth et al., 1969*

* Cuff
** Poultice
Δ 19/20 confidence limit
# undiluted unless specified

All tests for primary skin irritation have used rabbits as the experimental animal. The results parallel the chemical reactivities of the chloroethers. Four β-haloethers have been tested: bis(2-chloroethyl)ether, bis(2-chloroisopropyl)ether, 2-chloroethyl vinyl ether, and bis(2-chloroethoxy)methane. None caused even slight erythema when applied undiluted (Smyth et al., 1948, 1949, and 1951). CMME, however, caused "severe hyperemia, edema, denaturation, and even complete destruction of skin" when applied undiluted (Dow Chemical, no date). Similarly, BCME caused necrosis when applied undiluted (Smyth et al., 1969). Smyth and coworkers (1969) also indicate that BCME applied as a 10% solution in acetone caused "no reaction more severe than edema". However, because the haloether is unstable in acetone (Van Duuren et al., 1968), Smyth and coworkers (1969) may have underestimated its irritant properties.

c. Eye Injury

Eye irritation is occasionally cited as one of the effects of vapor exposure to the haloethers. No cases, however, note that these compounds cause severe eye injury. Carpenter and Smyth (1946) have developed a rather elaborate method for evaluating eye injury from direct contact with liquid solutions and subsequently tested five haloethers. Chemicals are ranked by injury grades of one to ten, ten being the most severe. Three of the β-chloroethers -- bis(2-chloroisopropyl)ether, bis(2-chloroethoxy)methane, and 2-chloroethyl vinyl ether cause damage approaching severe injury in rabbit eyes when 0.5 ml is applied undiluted [injury grade of 2] (Smyth et al., 1949, 1951, 1969). Bis(2-chloroethyl)ether, which has been reported to irritate eyes in humans at vapor concentrations of 2.5 ppm, causes damage approaching severe injury in rabbit eyes when 0.02 ml is applied undiluted and consistently causes severe injury when 0.1 ml is applied [injury grade of 4] (Carpenter and Smyth, 1946). BCME, the only α-chloroether tested, was by far the most damaging, causing severe injury when a 1% solution is applied to rabbit eyes [injury grade of 10] (Smyth et al., 1969). The solvent used in this test was not specified, but propylene glycol is the preferred solvent (Carpenter and Smyth, 1946). These results seem to indicate that direct eye contact with any of the chloroethers would be irritating and possibly damaging. As in skin irritation tests, the α-chloroethers are probably more potent than the β-chloroethers.

d. Acute Inhalation Toxicity

i) Chloroalkyl Ethers

Information on the acute inhalation toxicity of various haloethers is summarized in Table 33. The studies of Smyth, Carpenter, and coworkers are analogous to the oral and dermal exposures discussed above. The test animals are exposed once at a given concentration/duration, and mortality is noted over a two week observation period. Unlike the oral and dermal exposures, however, results from these acute inhalation studies do seem to present a gradient in terms of relative toxicity among the haloethers. With a single four hour inhalation exposure to rats, the α-haloethers are clearly more potent than the β-haloethers. Of the α-haloethers, BCME is about ten times more acutely toxic than its monofunctional analogue, CMME. A similar potency pattern is seen in inhalation carcinogenicity studies between these two compounds (see Section III-D-6, p. 126). Of the β-haloethers, bis(2-chloroethyl)ether and 2-chloroethyl vinyl ether seem about equally toxic. The somewhat disparate dose-response data for 2-chlorovinyl ether presented by Carpenter and coworkers (1949) and Smyth

Table 33. Acute Inhalation Toxicity of Haloethers

Compound	Organism	Conc. (v/v)	Duration	Response	Reference
Bis(chloromethyl)ether	Rats, (6), Carworth-Wistar, 4-5 weeks, 90-120 g	8 ppm 16 ppm	4 hrs. 4 hrs.	1/6 rats died in 14 day observation period 6/6 rats died in 14 day observation period	Smith et al., 1969
	Rats, Male, (10), Sprague Dawley, 8 weeks	0.94 ppm	7 hrs.	1 hamster and 4 rats with elevated lung-to-body weight ratios	Drew et al., 1975
	Hamsters, Male, (10), Golden Syrian, 6 weeks	>4.6 ppm	7 hrs.	Elevated lung-to-body weight ratios in 90% or more of rats and hamsters	
		7 ppm	7 hrs.	LC_{50} in 14 day observation period for rats and hamsters	
				[see text for details]	
Chloromethyl methyl ether	Rats	100 ppm	1/2 hr.	Highly irritating tumerous membranes	Dow Chemical, no date
		100 ppm	4 hrs.	"dangerous to life". Delayed death (days-weeks) usually from pneumonia	
		2000 ppm	1/2 hr.	" " " "	
	Rats, Male, Sprague Dawley, 8 weeks	55 ppm	7 hrs.	LC_{50}after 14 day observation period	Drew et al., 1975
	Hamsters, Male, Golden Syrian, 6 weeks	65 ppm	7 hrs.	LC_{50} after 14 day observation period	
				[see text for details]	
Bis(2-chloroethyl)ether	Rats, (6), Sherman	1000 ppm	3/4 hrs.	3/6 rats died in 14 days observation period	Smyth and Carpenter, 1948
	Rat, (6), Sherman, 100-125 g	250 ppm	4 hrs.	2-4/6 rats died in 14 day observation period	Carpenter et al., 1949
	Guinea Pigs	35 ppm	13.5 hrs.	Nasal irritation only	Schrenk et al., 1933
		105 ppm	13.5 hrs.	Respiratory depression and loss of motility. Death in 4/6 animals by 4 hrs. after exposure was terminated.	
		260 ppm	7.5 hrs.	Caused death in some animals	
		550 ppm	6 hrs.	Caused death in some animals	
		1000 ppm	4 hrs.	Caused death in some animals	
				[see text for details]	
Bis(2-chloroisopropyl) ether	Rats, (6)	1000 ppm	4 hrs.	1/6 rats died in 14 day observation period	Smyth et al., 1951
	Rats	120,000 ppm	immediate	Eye irritation and some incoordination	Dow Chemical, no date
		120,000 ppm	>1 hr.	Death in some animals	
	Rats	700 ppm	6 hrs.	Lethal dose; slight lung irritation and moderate to severe liver damage	
	Rats, (5)	350 ppm	8 hrs.	2/5 rats died. Moderate lung congestion and necrosis of the liver	
	Rats, (10)	350 ppm	6 hrs.	No deaths	
	Rats, (4)	175 ppm	8 hrs.	1/4 rats died	
2-Chloroethyl vinyl ether	Rats, (6), Sherman 100-150 g	250 ppm	4 hrs.	2-4/6 rats died in 14 day observation period	Carpenter et al., 1949
	Rats, (6), Sherman	500 ppm	4 hrs.	1/6 rats died in 14 day observation period	Smyth et al., 1949
Bis(2-chloroethoxy)methane*	Rats, (6), Carworth-Wistar, 4-5 weeks, 90-120 g	concentrated vapor	>1 hr.	Cause death in some animals	Smyth et al., 1969
Fluroxene(2,2,2-trifluoroethoxy ethene)	Mice, Male, (15), Swiss Weber, 25-30 g	45,000 ppm	0.5 hr.	No mortality	Cascorbi and Singh-Amaranath, 1972
	Ibid. (51)	45,000 ppm	1 hr.	8 mice (16%) died 16-30 hrs. after exposure	
	(15)	45,000 ppm	2 hrs.	100% mortality 16-30 hrs. after exposure	
				[see text for details]	
Methoxyflurane (2,2-dichloro-1,1-difluoro-1-methoxy ethane)	Rats, Male, (6), Fischer 344, 6 mo., 276-326 g	7,500 ppm	6 hrs.	Immediate gross hematuria in 4/6 rats Acute tubular necrosis in 2/6 rats	Mazze et al., 1972
				[see text for details]	

* Cited as Di(2-chloroethyl)acetal

and coworkers (1949) cannot be attributed to any obvious differences in experimental detail and, given the limited numbers of animals tested, may not be significant. In any event, the bis(2-chloroisopropyl)ether requires a two to four fold higher concentration to elicit a lethal response in rats comparable to either bis(2-chloroethyl)ether or 2-chloroethyl vinyl ether. Unlike bis(2-chloroethyl)ether, bis(2-chloroisopropyl)ether seems to have its primary effect on the liver rather than the respiratory tract. This distinction, however, is based on rather limited data. The concentrated vapor exposure to bis(2-chloroethoxy)methane is not readily compared to any of the above exposures because the actual concentration to which the animals were exposed is uncertain.

The much more detailed studies of Drew and coworkers (1975) and Schenk and coworkers (1933) are in approximated quantitative agreement with other corresponding studies summarized in Table 33 and support the general order of haloether inhalation potency outlined above.

Unlike the studies by Smyth, Carpenter, and coworkers which were designed to approximate relative orders of occupational hazard for a variety of synthetic chemicals, Drew and coworkers (1975) specifically addressed the acute toxicity of α-haloethers in conjunction with carcinogenicity testing. Single seven-hour exposures of both rats and hamsters to BCME or CCME resulted in similar pathological changes in the lungs of both species: i.e. congestion, edema, and hemorrhage. In addition single exposures to 12.5 - 255 ppm CCME produced dose-related increases in lung-to-body weight ratios, indicative of lung damage. Mortality at 14 days was also dose related. These details are summarized in Tables 34A and 34B.

In additional studies on BCME, both rats and hamsters were exposed to varying concentration for seven hours and observed until death. As in the above exposures, elevated lung-to-body weight ratios accompanied by congestion, edema, and hemorrhage were noted. The median life span of both species decreased in proportion to the haloether concentration (see Table 35).

Table 34. Mortality and Lung-to-Body Weight Ratios After Single Seven Hour Exposures to (A) Chloromethyl Methyl Ether and (B) Bis(chloromethyl)ether (Drew et al., 1975)

A: Chloromethyl methyl ether

	Rats(10)		Hamsters(10)	
Concentration, ppm	% Mortality at 14 Days	% Increased* Lung-to-Body Weight Ratio	% Mortality at 14 Days	% Increased* Lung-to-Body Weight Ratio
225	100†	80	100△	90
141	100	80	70	80
70	100	90	60	100
54	43	67	33	63
42	25	55	0	60
26	10	20	0	10
12.5	0	0	0	0

* Greater than control mean plus 3 SD
† All animals dead after four hours of exposure
△ Two animals dead during the exposure period

B: Bis(chloromethyl)ether

	Rats(90)		Hamsters(10)	
Concentration, ppm	% Mortality at 14 Days	% Increased* Lung-to-Body Weight Ratio	% Mortality at 14 Days	% Increased Lung-to-Body Weight Ratio
74	100	100	100	100
19	100	100	100	100
9	100	100	100	100
7.3	60	90	60	90
6.2	30	100	10	90
4.6	0	100	10	100
0.94	0	40	0	10

*Greater than control mean plus 3 SD

Table 35. Median Life Span and Lung-to-Body Weight Ratio after a Single Seven Hour Exposure to Bis(Chloromethyl)ether (Drew *et al.*, 1975)

Rats				Hamsters			
		Lung/Body Weight Ratio				Lung/Body Weight Ratio	
Concentration, ppm	Median Life Span, Days	Mean	% Above Normal*	Concentration, ppm	Median Life Span, Days	Mean	% Above Normal*
9.5	2	1.7	93	9.9	4	1.2	68
6.9	2	1.6	88	5.6	16	1.4	100
2.1	36	2.7	100	2.1	68	1.8	100
0.7	420	2.2	96	0.7	657	1.2	100
Control	462	0.6	...	Control	675	0.6	...

* Greater than control mean plus 3 SD

In this series of exposures, Drew and coworkers (1975) noted the relatively high mortality in rats at 6.9 ppm (median life span, 2 days) in contrast to the 14-day LC_{50} value of 7 ppm. This was attributed to the limited reliability of the calculated 14-day LC_{50} values because of the narrow range between no mortality (4.6 ppm) and complete mortality (9 ppm). Exposures of 2.1 ppm and above resulted in marked histopathological changes including tracheal and bronchial hyperplasia and squamous metaplasia without atypia. At 0.7 ppm, rats showed increases over controls in tracheal epithelial hyperplasia (36% in controls to 69% in exposed) and hamsters had increased pneumonitis (23% in controls to 67% in exposed). One hamster, dying at 770 days, had a focus of alveolar squamous metaplasia. In general, pathological damage was more severe in the longer surviving animals.

These single exposure studies thus indicate not only acute chemical irritation (edema, hemorrhage, and conjestion) but also epithelial changes perhaps related to α-haloether carcinogenicity (Drew et al., 1975).

Bis(2-chloroethyl)ether inhalation toxicity has been examined in some detail by Schrenk and coworkers (1933), with results in approximate agreement with those of Smyth and Carpenter (1948) and Carpenter and coworkers (1949). Here, it should be emphasized that Schrenk and coworkers (1933) present data on mortality occurring during exposure, unless otherwise specified, while the other investigators give mortality figures over a two week period after exposure. This difference may be particularly critical with the haloethers in that these chemicals seem to cause progressive damage over a prolonged period after exposure. This was noted above for the α-haloethers (Drew et al., 1975), and was also noted for the β-haloether. Gross pathological damage was similar to that caused by α-haloether exposure: lung conjestion, edema, and hemorrhage. In fatally exposed animals the degree of such damage was proportional to the length of time the animals survived, indicating progressive post-exposure damage. Conjestion of the kidney, liver, and brain was also noted but was perhaps secondary to lung damage. Detailed dose response data on bis(2-chloroethyl)ether is presented in Table 36.

Table 36. Effects of Bis(2-chloroethyl)ether on Guinea Pigs (Schrenk *et al.*, 1933).

Response	Period of exposure causing response with vapor concentration (a)				
	1000	550	260	105	35
Nasal irritation:					
Scratching at nose. . . .	(b)	(b)	1	2	3-10
Eye irritation:					
Squinting	(b)	(b)	1	20	c(810)
Lacrimation	1-2	1-2	3	c(810)	c(810)
Disturbance in respiration.	90	180	310	450	c(810)
Animals on slides; unable to stand; quiet; dyspnea; gasping respiration . . .	180-300	240-480	445-600	525-810	c(810)
Death	230-330	360-500	450-740	(d)	c(810)

a Concentration of vapor in ppm by volume; time in minutes

b Occurs immediately after start of exposure

c Not observed in the maximum exposure period given in parentheses

d Four died within a period ranging from immediately after to 250 minutes after exposure. Two survived 8 days and were killed for autopsy.

Besides the obvious difference in potency from the α-haloethers, the time course of post-exposure damage with bis(2-chloroethyl)ether may be different from that of the α-haloethers. For the α-haloethers (Drew *et al.*, 1975), no amelioration of lung damage, based on lung-to-body weight ratios, is noted even at low single dose levels after prolonged post-exposure observations (see Table 35). With bis(2-chloroethyl)ether, however, Schrenk and coworkers (1933) noted that the degree of conjestion from exposures not causing death initially increased but then markedly lessened eight days after exposure.

ii) Fluorinated Ethers

Along with information on the chloroalkyl ethers, Table 33 also summarizes two studies on the fluorine-containing ethers, fluroxene and methoxyflurane. Both of these fluorinated ethers, as indicated previously, are produced in relatively small quantities and used exclusively as anesthetics. Because of their medical applications, the pharmacology of these fluoroethers has undergone extensive investigation. Some of this information has already been discussed with reference to haloether metabolism. The development of these drugs and the continuing research on the anesthetic properties of other fluorinated ethers have generated biological data on scores of additional haloethers (e.g. Robins, 1946; Van Poznak and Artusio, 1960; Speers et al., 1971; Terrell et al., 1971). Krantz and Rudo (1966) provide a detailed review of much of this literature. While the biological effects of these fluorinated compounds are of undoubted interest to the medical community, a thorough review of this topic would not seem justified in an evaluation of the environmental threat posed by the commercially important haloethers. A cursory examination of the toxicity of fluroxene and methoxyflurane will illustrate this point.

Fluroxene was the first fluorinated anesthetic to be used in humans (Krantz and Rudo, 1966). As an anesthetic agent, its potency is similar to that of diethyl ether in dogs, producing satisfactory surgical anesthesia at 0.65 - 1.11 mg/kg and respiratory failure at 1.52 - 2.50 mg/kg with a mean anesthetic index of 2.35. After one hour exposures to anesthetic concentrations of fluroxene, dogs evidenced no change in liver function as measured by urinary elimination of bromosulfalein (Krantz et al., 1953). More recently, however, delayed death has been seen in dogs, cats, rabbits, and mice exposed to anesthetic concentration for more prolonged periods (Johnston and Thomas, 1971; Cascorbi and Singh-Amaranath, 1972). Cascorbi and Singh-Amaranath (1972) have shown that the duration exposure is critical to the number of delayed deaths in mice (see Table 33). These workers also found that no mortality was produced in mice given a dose schedule of 4.5% fluroxene x 1/2 hr./day x 3 days, whereas 50% mortality was elicited in mice given two exposures of 4.5% fluoroxene x 1 hr. with 48 hours between exposures. In addition, inhibition of drug metabolizing enzymes with carbon tetrachloride eliminated delayed death from an otherwise lethal dose of fluroxene. Conversely, stimulation of drug metabolizing enzymes with phenobarbital resulted in 95% mortality after exposure to an otherwise nonlethal dose of fluroxene. These observations indicate that a metabolite of fluroxene is the toxic agent (Cascorbi and Singh-Amaranath, 1972). As previously discussed (see Section III-B, p. 83), this agent may be trifluoroacetic acid (Cascorbi and Singh-Amaranth, 1973).

Although the precise nature of the toxic response was not determined in the above studies, Harrison and Smith (1973) have demonstrated that a normally nonlethal 3 hour exposure to fluroxene results in massive lethal hepatic necrosis in rats whose liver cytochrome P-450 levels had been increased with phenobarbital. Thus, fluroxene toxicity may be similar to halothane ($CF_3\text{-}CC\ell BrH$) -- which is also metabolized to trifluoroacetic acid -- and hepatotoxicity is probably the primary adverse effect (Van Dyke, 1973).

Methoxyflurane, on the other hand, primarily affects the kidneys. Mazze and coworkers (1972) have shown that methoxyflurane affects rat kidney function and histology in a dose-related manner. At the highest dose level tested (0.75% x 6 hrs, see Table 33), four of six rats developed gross hematuria attributable to severe hemorrhagic and ulcerative cystitis of the bladder, and one rat developed polyuria followed by oliguric renal failure. Histological examinations of the renal cortices of these rats revealed dilation of the convoluted tubles, reduced height of littoral cells, deposits of calcium oxalate crystals, and foci of increased eosinophil leukocytes, fragmented or condensed nuclei, and intraluminal slough of necrotic tubular epithelial cells. Two of the six rats had acute tubular necrosis. As with fluroxene, metabolites of methoxyflurane are the toxic agents. Of these, inorganic fluoride is probably the most nephrotoxic (Van Dyke, 1973), while oxalic acid may cause renal inflammation and scarring due to crystal formation (Mazze _et al_., 1972). Also like fluroxene, stimulation of liver cytochrome P-450 with phenobarbital potentiates the toxic action of methoxyflurane (Cousins _et al_., 1973).

iii) Toxicological Relationships between the Chloroalkyl Ethers and Fluorinated Ethers

As indicated previously, the metabolism of the chloroalkyl ethers is poorly understood. As should be apparent from the above discussion on acute toxicity, the mechanism of action of these chloroethers has received little attention. In contrast, the fluorinated ethers have been examined in detail. Thus, a detailed comparison of these two groups of chemicals is neither warranted nor possible. However, a few elementary points deserve emphasis.

Fluorination radically alters the chemical and toxicological properties of aliphatic compounds (Clayton, 1966; Howard et al., 1974). While both diethyl ether and fluoroxene may have similar anesthetic potencies and while both may cause death due to respiratory failure at high concentrations, only fluroxene is specifically hepatotoxic. Similarly, while further toxicological testing might conceivably demonstrate hepato- or nephrotoxicity for some of the chloroalkyl ethers, this would not be directly related to fluroxene or methoxyflurane toxicity as currently understood.

Based on available information, the biological activity of the α-chloromethyl ethers has no relationship to the fluorinated ethers. The former are highly reactive and corrosive respiratory irritants and carcinogens. It seems probable that they alkylate or hydrolyze in the respiratory tract and are not subject to absorption as such, and hence would not directly effect internal organs other than the respiratory tract itself. The β-chloroethers may be similar to the fluorinated ethers only in that they are stable enough to be absorbed, metabolized, and cause organ specific effects. In acute inhalation exposures, they act primarily as respiratory irritants like the α-chloroethers. Their biological effects under other conditions are discussed in appropriate sections. Thus, because information on these fluoroethers is of negligible use in understanding the biological effects of the commercially significant chloroalkylethers, the abundant toxicological data on these fluorinated compounds are not reviewed in detail in this report.

2. Chronic Toxicity

a. Chronic Oral Toxicity

Only two haloethers have been tested in repeated oral administration, bis(2-chloroethyl)ether and bis(2-chloroisopropyl)-ether. The maximum dose of bis(2-chloroethyl)ether causing no mortality to male and female one-week old mice after nineteen daily doses by stomach tube was determined as part of a carcinogenicity screening program (see Section III-D-6, p. 126), and was found to be 100 mg/kg (Innes et al., 1969). This daily dose is only slightly less than the single oral dose (136 mg/kg) found to be lethal to half the exposed mice over a two week observation period after administration (Spector, 1956; Table 31).

Similar results are evident with bis(2-chloroisopropyl)ether. Twenty-two doses over a thirty one day period at 200 mg/kg administered to rats by stomach tube reduced growth rates, increased the weight of liver, kidney, and spleen relative to total body weight, but had no effect on hematology and caused no deaths. Administration of 10 mg/kg on the same schedule caused only a reduced growth rate (Dow Chemical, no date).

As indicated in Table 31, this same study, presumably using the same strain rats under similar conditions, found that a single administration of 400 mg/kg was lethal to four of six rats tested. Further, Smyth and coworkers (1951) note that a single administration of 240 mg/kg bis(2-chloroisopropyl)ether causes death in half the exposed rats over a two week observation period.

Because of the lack of detail in both the acute and chronic studies, these results are difficult to interpret. From the available data, these β-chloroethers seem to have a relatively narrow range between concentrations causing death and concentrations causing no marked effects. The chloroethyl ether seems somewhat more toxic than the chloroisopropyl ether, and the concentration seems more critical than the frequency of exposure. This pattern is consistent with a chemical that is readily absorbed and then rapidly detoxified and/or eliminated.

b. Chronic Dermal Toxicity

All repeated dermal applications of haloethers have been conducted by Van Duuren and coworkers (1968 and 1969) in setting dose levels for long term carcinogenicity screening tests.

These dose setting tests involved applying varying amounts of the haloethers to the shaven dermal skin of eight week old female mice (ICR/Ha Swiss) three times a week for two weeks. The maximum tolerated dose was established as the highest dose producing no adverse effects (e.g. ulcerative lesions). Four haloethers were thus tested: BCME, CMME, α,α-dichloromethyl methylether, and bis(2,3,3,3-tetrachloro-n-propyl)-ether. For all of these compounds, the maximum tolerated dose was determined to be 2 mg haloethers in 0.1 ml of benzene.

All of these haloethers were subsequently applied at the same level and frequency over prolonged periods, BCME and CMME for 325 days and the other haloethers for 540 days. In these exposures, BCME resulted in epilation and edema of subcutaneous tissue. This is apparently similar to the effect on rabbits noted for a single application for unspecified quantity of undilute chloromethyl ether (see Table 32). In these long term studies on mice, however, only the BCME produced obvious skin damage.

c. Chronic Toxicity of Haloethers in Subcutaneous Injection

Multiple subcutaneous injections of haloethers parallel the chronic dermal exposures both in purpose and methodology. Maximum tolerated doses of 3 mg (Per animal per injection) were determined for BCME and CMME using six week old female rats (Sprague Dawley). However, neither the frequency nor duration of these "short term" toxicity tests are noted. As in the dermal studies, prolonged exposure [3 mg/injection, 1 injection/week x 114 days] to BCME resulted in severe ulceration at the injection site. This effect persisted and was accompanied by significant weight loss even after the dose was dropped to 1 mg/injection and the frequency reduced to thrice monthly. The total treatment period lasted about 300 days. CMME [3 mg/injection, 1 injection/week x ∿ 300 days] produced similar but less pronounced effects (Van Duuren _et al_., 1968).

Analogous tests have been conducted using CMME, bis(1-chloroethyl)ether, and bis(2-chloroethyl)ether on six week old female mice (ICR/HA Swiss). Again, frequency and duration of injection for the "short term" toxicity tests are not specified. In these tests, the highest dose which caused minimum cytotoxic effects was determined to to be 0.3 mg for both CMME and bis(1-chloroethyl)ether, and 1 mg for bis(2-chloroethyl)ether (Van Duuren _et al_., 1972). Presumably, these tests involved only histological examination at the injection site. The lower toxicity of bis(2-chloroethyl)ether by this route is consistent with the much greater chemical reactivity of the α-haloethers as opposed to the β-haloethers and with the premise that the mode of action, both in skin irritation and carcinogenicity, is related to the alkylating ability of these compounds.

d. Chronic Inhalation Toxicity

Multiple inhalation exposures reflect the recent concern with the occupational carcinogencity hazard posed by

BCME and CMME. Both of these α-haloethers have been tested in some detail. Of the β-haloethers, only bis(2-chloroethyl)ether has been examined. All of these exposures are summarized in Table 37 and agree with the view of haloether toxicity presented in the previous section -- i.e. that the α-haloethers are more chemically reactive and hence more corrosive and toxic than the β-haloethers.

Table 37. Chronic Inhalation Toxicity of Haloethers

Compound	Organism	Conc. (v/v)	Exposure Period	Frequency	Duration	Response	Reference
Bis(chloromethyl)ether	Rats, Male, 120 Sprague Dawley	0.01 and 0.001 ppm	6hr/day	5days/ week	6 months	no increased mortality	Leong et al., 1975
		0.1 ppm	6hr/day	5days/ week	6 months	increased mortality [see text]	
	Mice, Male, 144-160, Swiss Webster	0.01 and 0.0001 ppm	6hr/day	5days/ week	6 months	apparent increase in mortality [see text]	
		0.1 ppm	6hr/day	5days/ week	6 months	increased mortality [see text]	
	Rats, Male, 20-50, Sprague Dawley	0.1 ppm	6hr/day		10-100 exposures	decreased median life span in rats receiving 80 and 100 exposures [see text for details]	Kuschner et al., 1975
	Rats, Male, 50 Sprague Dawley, 8 weeks	1 ppm	6hr/day		3, 10, & 30 exposures	100% mortality after 30 exposures Rats and Hamsters: Increase in broncheal and tracheal hyperplasia and squamous metaplasia. Decreased median life span [see text for details]	Drew et al., 1975
	Hamsters, Male, 50, Golden Syrian, 6 weeks	1 ppm	6hr/day		3, 10, & 30 exposures		
	Mice, Male, 50 A/Heston 20-25 g.	1 ppm	6hr/day	5days/ week	82 exposures in 27 weeks	37 mice died. Loss of body weight, respiratory distress; hemorrhage, and patchy consolidation of lungs	Leong et al., 1971
Chloromethyl methyl ether	Rats, Male, 25 Sprague Dawley 8 weeks	1 ppm	7hr/day		30 exposures	2 rats died on days 16th and 22nd exposures	Drew et al., 1975
		10 ppm	7hr/day		30 exposures	22 rats died on day from 3rd to 30th exposures [see text for details]	
	Mice, Male, 50 A/Heston, 20-25 g.	2 ppm	6hr/day	5days/ week	101 exposures in 21 weeks	mortality, body weight, and demeanor not significantly different from controls	Leong et al., 1971
Bis(2-chloroethyl)-ether	Rats and Guinea Pigs	69 ppm	7hr/day	5days/ week	93 exposures in 130 days	significant growth depression noted in males of both species. No other adverse effects noted in appearance, behavior, mortality, hematology, and gross or microhistology	Dow Chemical, no date

As in acute inhalation exposures, BCME is clearly the most toxic of the haloethers. As indicated in Table 37, multiple exposures to BCME have been conducted at 1 ppm and 0.1 ppm, six hours per day. Of the mammals tested, the mice used by Leong and coworkers (1971) seem the most resistant showing only 74% mortality after 82 exposures over 2.7 weeks. Both rats and hamsters, however, reached 100% mortality prior to ten weeks after only 30 exposures to 1 ppm. As illustrated in Table 38, rats seem more severely effected than hamsters in terms of decreased longevity.

Table 38. Median Life Span of Rats and Hamsters After Multiple Exposures to 1 ppm Bis(chloromethyl)ether (modified from Drew et al., 1975).

	Rats		Hamsters	
Number of Exposures	Median Life Span (days)	% of Control	Median Life Span (days)	% of Control
30	23	5%	42	6.2%
10	21	4.5%	137	20%
3	168	36%	471	70%
0	462	100%	675	100%

Even at a ten-fold liver concentration, both rats and hamisters experience decreased median life spans. As partially summarized in Table 37, rats exposed to 0.1 ppm BCME for six hours per day for 80 and 100 exposures had median life spans of forty-three and fifty weeks, respectively (median life span of control group was sixty-six weeks). In addition, both rats and hamsters show markedly increased mortality over control groups during life time exposures to 0.1 ppm BCME for six hours per day (see Figures 19 and 20).

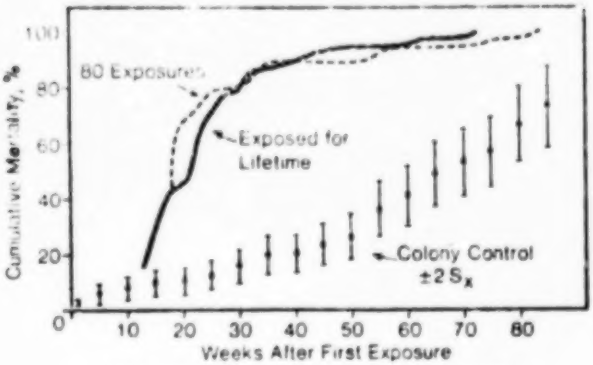


Figure 19. Mortality of Rats Following Chronic Exposures to 0.1 ppm Bis(chloromethyl)-ether (Kuschner *et al.*, 1975)

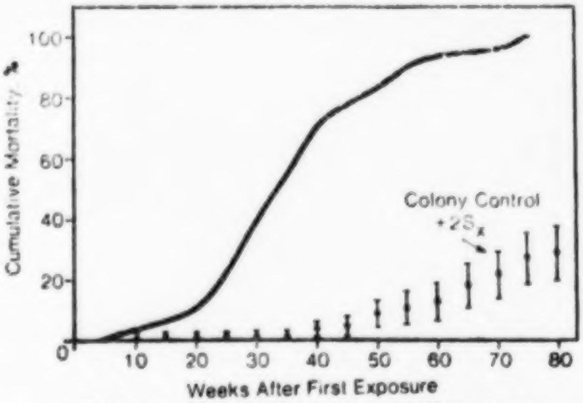


Figure 20. Mortality of Hamsters Following Chronic Exposures to 0.1 ppm Bis(chloromethyl)ether (Kuschner *et al.*, 1975)

Leong and coworkers (1975) examined the effects on rats and mice of repeated exposures of 0.1, 0.01, and 0.001 ppm BCME. Similar to the results of Kuschner and coworkers (1975), rats exposed to 0.1 ppm BCME for 6 hours/day, 5 days/week x 6 months showed a marked increase in mortality starting one month after exposure terminated. By the eleventh month after exposure terminated, virtually all of the 0.1 ppm exposed rats had died while the control group had only 26% mortality. Rats exposed to 0.01 and 0.001 ppm BCME had mortality patterns similar to the control group throughout the twenty-seven month study period. Both the control and exposed mice in this study suffered from ascending urinary tract infection which appeared to be the direct cause of death in most mice. Thus, while the mortality patterns of the various exposure groups did show an apparent concentration related effect (see Figure 21), the precise role of BCME is uncertain.

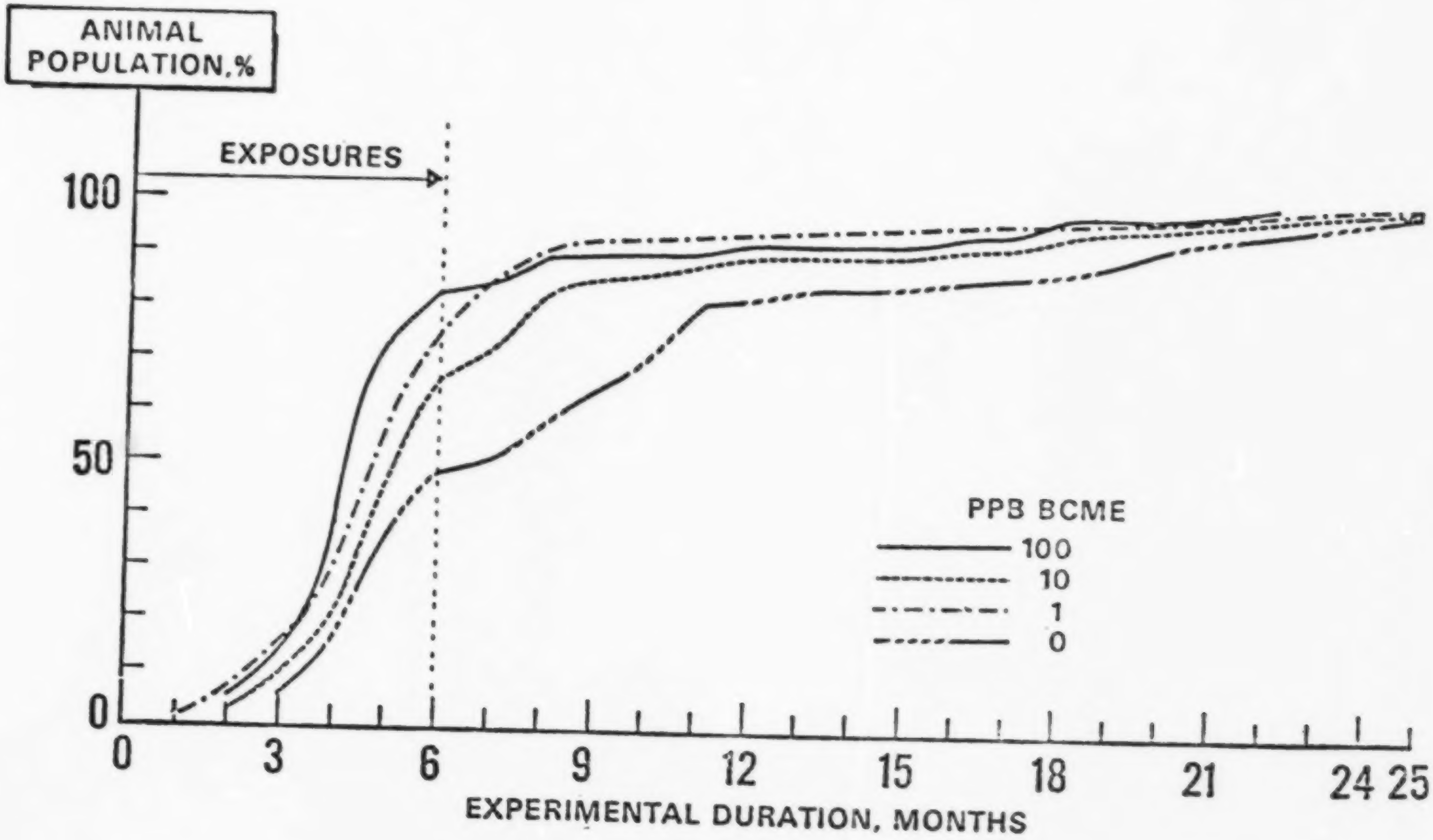


Figure 21. Cumulative Percent Mortality of Male Mice Exposed to Bis(chloromethyl)ether (Leong *et al.*, 1975)

The lung pathology in mice after multiple exposure to BCME noted in Table 37 is similar to that seen in rats and hamsters after acute exposures (see Table 37) and is indicative of the corrosive effects of this chemical (Leong et al., 1971). In rats, multiple exposures to BCME evidenced dose related increases in bronchial tracheal hyperplasia and bronchial squamous metaplasia. Atypias, mostly abnormal nuclei, were noted in all of these pathological changes but were not dose related. Similar pathology was seen in hamsters with dose related increases in bronchial hyperplasia with and without atypia. Extreme irritability, subarachnoid hemorrhage, and other signs of central nervous systems effects were seen in animals of both species exposed ten or more times to BCME.

At exposure conditions under which BCME causes marked lethality, CMME has a much less pronounced effect. As indicated in Table 37, CMME at 1 ppm, 7 hrs/day x 30 exposures resulted in only 8% mortality in rats while a nearly identical exposure to BCME caused 100% mortality. Only at 10 ppm did CMME cause deaths in nearly all test rats (Drew et al., 1975). This agrees well with acute inhalation data previously cited indicating that BCME is about ten times as toxic as CMME, by this route. Mice respond similarly to CMME, as compared to BCME, showing no gross toxic response to 101 exposures to the monochloroether at 2 ppm, whereas the dichloroether produced 74% mortality with fewer exposures and at one half the concentration (Leong et al., 1971, see Table 37).

Lung pathology is similarly less severe with CMME. In the 1 ppm exposure to rats (Drew et al., 1975), only one in five rats examined immediately after the thirtieth exposure had slight hemorrhage of both lungs, the remaining four having no lung abnormalities. Even in the 10 ppm exposure, the only common change noted was regenerative bronchial hyperplasia which was seen in 40% of the rats. As in acute exposures, deaths in this group were associated with increased lung-to-body weight ratios. Of the mice repeatedly exposed to 2 ppm CMME, the lungs of eleven animals had pin-point hemorrhage or patchy consolidation (Leong et al., 1971).

No details are given for the exposure of rats and guinea pigs to bis(2-chloroethyl)ether other than those noted in Table 37. As in acute exposures, the β-haloether seems much less toxic than either of the α-haloethers.

3. Sensitization - No studies encountered.

4. Teratogenicity

The commercially important chloroethers have not been tested for teratogenicity. The anesthetic haloether methoxyflurane, however, has been found to induce congenital abnormalities in C57 black mice. When exposed to 0.3% methoxyflurane, three hours per day, on days 10-12 of gestation, 45% of the surviving group had skeletal abnormalities. The release of free fluoride ions is thought to be the causative factor (Smith, 1974). Thus, this effect cannot be considered indicative of the chloroethers.

5. Mutagenicity

None of the chloroethers have been tested as mutagens in mammals. However, BCME and CMME have been cited as mutagens in bacteria (see Section III-G, p. 148).

6. Carcinogenicity

a. Screening Tests

Since the initial indication by Van Duuren and coworkers (1968) that BCME exposure leads to an increased incidence of carcinoma in mice, a variety of haloethers and related compounds have been screened for carcinogenicity. Although some studies have involved oral administration or inhalation, most of the screening tests have utilized dermal application or subcutaneous injection. Because the experimental design varies considerably with the mode of exposure, the results of the various investigations are detailed by route of administration.

(i) Dermal Application

The greatest number of haloethers have been tested for carcinogenicity by applying solutions of haloethers in an appropriate solvent to the shaven backs of mice. Because the haloethers degrade when dissolved in acetone, benzene has been used as the haloether solvent in all dermal applications (e.g., Van Duuren _et al_., 1969). Three types of carcinogenic activity have been examined: complete carcinogenesis, initiating activity, and promoting activity. Tests for complete carcinogenesis simply consist of exposure to the test compound at regular intervals - usually three times each week - over a relatively prolonged period - approximately one year. Initiating and promoting activity refers to the process of two-stage carcinogenesis. In tests for two-stage carcinogenesis, the animal is exposed once to the initiating agent; after a period of usually two weeks, the animal is exposed repeatedly (usually three times per week) to the promoting agent. A compound may be classified as an initiating agent if a single application of the compound followed by repeated applications of a known promoting agent leads to significant increase in tumor production. Conversely, a compound is classified as a promoting agent if repeated applications of the compound, after previous exposure to a known initiating agent, lead to a significantly increased incidence of tumors. The criteria for "significant increase" production by haloethers is usually based on a comparison to known carcinogenic alkylating agents (certain epoxides or lactones) or to a positive control (known initiating agent and promoting agent) and negative control. The critical aspect of two-stage carcinogenesis testing is that neither the initiating agent nor the promoting agent, when used alone at test doses, results in an appreciable incidence of tumor production.

In evaluating the effects of dermal exposure, two types of neoplasms are noted: squamous papillomas and squamous cell carcinomas. Squamous papillomas are benign growths on the epidermis which may either regress, persist, or become malignant. Squamous cell carcinomas are malignant growths which infiltrate into the dermis and/or metastasize. Histologically, both neoplasms evidence epidermal hyperplasia and hyperkeratosis (Van Duuren et al., 1968). The results of dermal application of various haloethers are summarized in Table 39.

Of the haloethers tested as whole carcinogens - promoting agent with no initiating agent in Table 39 - only BCME shows any positive activity. This compound is carcinogenic under test conditions, producing papilloma in thirteen of twenty mice, twelve of which subsequently developed squamous cell carcinomas (Van Duuren et al., 1969). Similarly, in

Table 39. Tumor Induction in Mice Involving Dermal Application of Various Haloethers

Initiating Agent		Promoting Agent①				Observation Period (days)	Number of Mice Strain Sex, Age	PAPILLOMAS#			CARCINOMAS#			Median Survival Time (Days)	Reference
Chemical	Dose	Chemical	Dose	Application per week	Duration (days)			M(N)	$\bar{X}$	T	M	$\bar{X}$	T		
None	-	Bis(chloromethyl)* ether	2mg	3	325	540	20, ICR/HA Swiss, Female, 8 weeks	13	(0.65)	161	12	0.6	231	313	Van Duuren et al., 1969
Benzo(a) pyrene	0.15mg	"	2mg	3	325	540	" "	13	(0.65)	98	12	0.6	196	315	" "
Bis(chloro-methyl)ether	1mg	Phorbol ester	0.025mg	3	540	540	" "	5	(0.25)	76	2	0.1	N.S.	474	" "
" "	1mg	Acetone (solvent control)	0.1ml	3	540	540	"	0	0	-	0	0	-	>540	" "
" "	1mg	None	-	-		540	" "	0	0	-	0	0	-	>540	
" "	1.05mg "	Croton oil "	0.05ml "	2 "	210	105 210	27, Charles River CD1, Female, 7-9 wks.		0.4 0.3						Slaga et al.② 1973
" "	2.1mg	Croton oil	0.05ml	2	210	105 210	28, " "		0.9 0.6						" "
" "	2.1mg	None	-	-	-	105 210	30, " "		0 0						" "
None	-	Chloromethyl methyl ether	2mg	3	325	325	20, ICR/HA Swiss, Female, 8 weeks	0	0	-	0	0	-	>540	Van Duuren et al., 1969
Benzo(a) pyrene	0.15mg	Chloromethyl methyl ether	2mg	3	325	540	" "	1	(0.05)	392	0	0	-	>540	" "
Chloro-methyl methyl ether	0.1mg	Phorbol ester	0.025mg	3	540	540	" "	7	(0.35)	259	4	.2	N.S.	496	" "
" "	1.0mg	Phorbol ester	0.025mg	3	540	540	" "	5	(0.25)	160	1	.05	N.S.	488	" "
" "	1.0mg	Acetone (solvent control)	0.1ml	3	540	540	" "	0	0	-	0	0	-	>540	" "
" "	0.1mg	None	-	-	-	540	" "	0	0	-	0	0	-	>540	" "
" "	1.0mg	None	-	-	-	540	" "	0	0	-	0	0	-	>540	" "
" "	1.0mg	Croton oil	0.05ml	2	210	105 210	28, Charles River, CD1, Female, 7-9 weeks		0 0						Slaga, et al② 1973
" "	2mg	Croton oil	0.05ml	2	210	105 210	30, " "		0.1 0						" "
" "	4mg	Croton oil	0.05ml	2	210	105 210	30, " "		0.1 0.1						" "
" "	10mg	Croton oil	0.05ml	2	210	105 210	30, " "		0.1 0.2						" "
" "	2mg	None	-	-	-	105 210	29, " "		0 0						" "
None		α,α-Dichloro-methyl methyl ether	2mg	3	450	450	20, Swiss Millerton, Female, N.S.	0	0	-	0	0	-	>650	Van Duuren et al., 1969
Benzo(a) pyrene	0.15mg	α,α-Dichloro-methyl methyl ether	2mg	3	450	450	" "	0	0	-	0	0	-	>650	" "
α,α-Dichloro-methyl methyl ether	1.0mg	Phorbol ester	0.025mg	3	450	450	" "	3	(0.15)	187	1	.05	N.S.	>650	" "
Bis(1-chloro-ethyl) ether	1mg	Phorbol myri-state acetate	2.5μg	3	590	590	20, ICR/HA Swiss, Female, 6 weeks	7(9)	(0.45)	61	0	0	-	414	Van Duuren et al., 1972
" "	1mg	Acetone (solvent control)	0.1ml	3	590	590	" "	0	0	-	0	0	-	>582	" "
Bis(2-chloro-ethyl) ether	1mg	Phorbol myri-state acetate	2.5μg	3	590	590	20, ICR/HA Swiss, Female, 6 weeks	3(3)	(0.15)	202	0	0	-	459	Van Duuren et al., 1972
" "	1mg	Acetone (solvent control)	0.1ml	3	590	590	" "	0	0	-	0	0	-	>593	" "
None	-	Octachloro-di-n-propyl ether	2mg	3	450	450	20, Swiss Millerton, Female, N.S.	0	0	-	0	0	-	>450	Van Duuren et al., 1969
Benzo(a) pyrene	0.15mg	Octachloro-di-n-propyl ether	2mg	3	450	450	" "	1	(0.05)	223	0	0	-	>450	" "
Octachloro-di-n-propyl ether	1mg	Phorbol ester	0.025mg	3	450	450	" "	3	(0.15)	321	1	.05	N.S.	>450	" "

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Key to Table

# M = number of mice with papillomas or carcinomas

N = total number of papillomas or carcinomas

$\bar{X}$ = number of papillomas or carcinomas per mouse. Number in ( ) assume N=M

t = time to first papillomas or carcinomas

① Two week period between initiation and promotion unless otherwise specified

② One week period between initiation and promotion unless otherwise specified those haloethers tested as promoting agents - using benzo(a)pyrene as initiating agent - BCME is again the only compound with clear carcinogenic action. The only effect of the initiating agent for this haloether is to decrease the period before neoplasms appear without altering the incidence of papilloma and carcinoma development. CMME and octachloro-di-n-propyl ether did result in papilloma development in one of twenty mice in each experimental group, but these papillomas did not develop into carcinomas and the mean survival time of the experimental groups was not reduced. The activity of these latter two haloethers is comparable to a control group using benzo(a)pyrene as an initiator and acetone (a skin irritant but noncarcinogenic) as the promoting agent, and, thus, they are not considered to be carcinogenic promoting agents in this series of tests (Van Duuren et al., 1969).

As indicated in Table 39, the majority of dermal exposures have tested haloethers as initiating agents. This method is particularly suitable for the more caustic haloethers (e.g., BCME and CMME) which are not tolerated on repeated application (Van Duuren et al., 1969; also see Section III-D-2-b, Chronic Dermal Toxicity, p. 117).

As in whole carcinogen and promoting tests, BCME shows positive initiating activity. In the work of Van Duuren and coworkers (1969), one treatment with BCME followed by phorbol ester promotion resulted in papillomas in five of twenty exposed mice, two of which subsequently developed squamous cell carcinomas with metastasis to the lung in one mouse. The first tumor in this group was observed after seventy-six days. In contrast, a negative control group of twenty mice receiving phorbol ester promotion without an initiating agent developed only two papillomas, the first of which did not appear until the three hundred and twenty second day of treatment, and neither of which progressed to carcinomas. Conversely, the initiating activity of BCME is well below that of the benzo(a)pyrene-phorbol ester (positive control) group in which all twenty exposed mice developed papillomas (the first within seventy days) and seven subsequently developed carcinomas. Thus, the initiating activity of BCME is appreciably higher than the negative controls but only moderate in comparison to the potent carcinogen benzo(a)pyrene. Further, as indicated in Table 39, an initiating dose of BCME failed to produce any neoplasms in the absence of phorbol ester promotion.

These results are in substantial agreement with the more recent work of Slaga and coworkers (1973) when differences in experimental technique are considered. Using a comparable initiating dose of BCME followed by croton oil promotion, Slaga and coworkers (1973) note a 0.4 incidence of papilloma development per mouse at 105 days with 25% of these regressing by 210 days. No carcinomas are noted. While these investigators used a different strain of mice than that used by Van Duuren and associates (1969), it seems probably that the papilloma regression is partially due to the use of croton oil rather than phorbol esters as the promoting agent. Although both promoting agents are derived from the seeds of Croton tigluim L. (Van Duuren and Orris, 1965) and have enjoyed wide used as promoting agents in two-stage carcinogenesis testing, croton oil is a less refined extract which has been shown to result in more tumor regressions and fewer malignancies than purified phorbol esters (see Van Duuren, 1969, for complete review of croton-based promoting agents). This alone, however, may be too simplistic an explanation. Using initiating doses (e.g., producing no tumor promotion) of urethane with croton oil promotion, levels of papillomas at 105 days in mice were about identical to those produced by BCME but increased rather than regressed at 201 days (Slaga _et al_., 1973). No carcinomas were noted in urethane treated mice, although urethane is generally regarded as a potent carcinogen. Thus, the tumor regression and lack of carcinoma development noted in BCME initiation is probably attributable to both the limited promoting activity of croton oil and the moderate rather than potent initiating activity of the haloether. The central point, however, is apparent: BCME has definite pronounced initiating activity. This is demonstrated in the almost quantitative increase in papilloma incidence at both 105 and 210 days when the initiating dose of the haloether is doubled (see Table 39). As in the study by Van Duuren and coworkers (1969), BCME failed to induce papillomas when the active promoting agent was omitted (Slaga _et al_., 1973).

Similar to the above work on BCME, the same groups of investigators have screened CMME as an initiating agent. Although inactive as a whole carcinogen and promoting agent, CMME (>99.5% pure) showed definite initiating activity with phorbol ester promotion when tested by Van Duuren and coworkers (1969), producing a marked increase in papillomas over phorbol ester control as well as leading to carcinomas - not found in phorbol ester controls - in five of the forty mice tested at two dose levels (see Table 39).

The total incidence of tumor production was inversely related to haloether dose, but the higher dose did result in a decreased latent period to papilloma appearance. As with BCME, CMME was markedly less potent as an initiator than benzo(a)pyrene and had no activity in the absence of an active promoting agent (Van Duuren et al., 1969). In the test conducted by Slaga and coworkers (1973), CMME showed only slight initiating activity at doses two to ten times higher than those used by Van Duuren and coworkers (1969). The difference already discussed between these two series of tests may have contributed to this disparity. Although the incidence of papillomas and the degree of papilloma persistence is directly proportioned to the dose of CMME in the study by Slaga and coworkers (1973), the investigators did not consider this haloether to be an effective initiator. Control data on mice receiving croton oil promotion alone is not given to support this conclusion, but supportive biochemical evidence is detailed below (see Section III-D-6-b, p. 145).

None of the remaining haloethers listed in Table 39 can be considered as potent as BCME or CMME. Bis(1-chloroethyl)ether, however, does shown some activity. Although no carcinomas were produced by this haloether, nine papillomas were induced in seven of twenty mice, and most important, the time to this appearance of the first papillomas was only sixty-one days. This is appreciably higher than the phorbol myristate acetate (promotor) control wihch produced only two papillomas in two mice, the first tumor appearing after three hundred and forty seven days (Van Duuren et al., 1972). In groups of twenty mice exposed to bis(2-chloroethyl)ether, α,α-dichloromethyl methyl ether, or octachloro-di-n-propyl ether, three mice in each group developed papillomas, and one mouse in each of the latter two groups developed carcinomas: this activity, however, is considered negligible compared to promotor controls and the relatively long latent periods to neoplasm appearance (Van Duuren et al., 1969 and 1972).

(ii) Subcutaneous Injection

Two types of studies have been conducted on the effects of subcutaneous injection of haloethers in laboratory mammals. One type (i.e., Gargus et al., 1969) involves a single injection of the haloether as the only treatment, followed by histological examination of the lungs and any other grossly abnormal tissue after six months. In the other type (i.e., Van Duuren et al., 1969 and 1972), the animals receive injections repeated once weekly for a period of 300-658 days followed by histological examination of the injection site and any abnormal tissues. Tumors associated with haloether exposure are found only at the injection site or the lung. Both benign fibroma, adenoma - and malignant - sarcoma, fibrosarcoma - tumors have been induced. The results of these studies, along with other appropriate details, are given in Table 40.

As in the dermal application studies, BCME shows marked tumorogenic activity. On repeated injections, five of twenty exposed rats developed fibrosarcomas at the injection site with two additional rats developing fibromas. Of particular note is the short period, fifty-eight days, before the first fibrosarcoma appeared. No tumors beyond the injection site were associated with haloether exposure (Van Duuren et al., 1969). The active

Table 40. Tumor Induction Associated with Subcutaneous Injection of Various Haloethers into Mice and Rats

Chemical	Total Dose/ Injection	mg/kg/ First Injection	Vehicle, Amount	Frequency of Injection	Site of Injection	Animal, Strain, Sex, Age, Wgt	Number of Animals	Number of Animals with Tumors, Type, Site	X Number of Animals with Tumors/Number of Animals Exposed	N Number of Tumors/Total Number of Animals	Time to First Tumor	Median Survival Time (Days) for All Test Animals	Reference
Bis(chloro-methyl)ether	3mg	25mg/kg	Nujol, 0.1ml	1/wk x 114 days followed by [illegible] days	Left Axillary Area	Rats, Sprague-Dawley, Female, 9wks, 120-125gr	20	1, Benign Fibromas, Inj. Site	0.05 (1/20)	0.05	N.S.	325	VanDuuren et al., 1969
" "	1mg	8mg/kg	Nujol, 0.1ml					5, Malignant Fibrosarcomas, Inj. Site 1, Fibroadenoma, Breast (NAE)*	0.25 (5/20)	0.25	58	325	
" "	0.036mg	12.5-13/kg (15mg/kg)	Peanut oil, 0.05ml	Single Injection	Middorsal Area	Mice, ICR Swiss, Female, 24-72hrs., ~2gr	50	20, Adenomas, Lung	0.40 (20/50)	0.47 (23/50)	N.S., results given 6 mo. after injection	N.S.	Gargus et al., 1969
" "						Ditto, Male	50	29, Adenomas, Lung	0.58 (29/50)	0.82 (41/50)			
								1, Papilloma and 1 Fibrosarcoma found at injection site, not seen in 600 controls. Sex not specified.					
Chloromethyl methyl ether	0.3mg	10mg/kg	Nujol, 0.03ml	1/wk x 685 days	Left Flank	Mice, ICR/HA Swiss Female, 6 weeks, wgt. N.S. (assume 30gr.)	30	10, Sarcomas, Injection Site	0.33 (10/30)	0.33 (10/30)	308	496	VanDuuren et al., 1972
" "	3mg	24mg/kg	Nujol, 0.1ml	1/wk x 300 days	Left Axillary Area	Rats, Sprague-Dawley, Female, 9wks, 120-125gr	20	1, Malignant Fibrosarcoma, Inj. Site	0.05 (1/20)	0.05 (1/20)	N.S. after 300	478	VanDuuren et al., 1969
" " containing 0.3-2.6% bis-(chloromethyl)-ether	0.35mg	125-175/kg (175mg/kg)	Peanut oil, 0.05ml	Single Injection	Middorsal Area	Mice, ICR Swiss, Female, 24-72hrs., ~2gr	48	8, Adenomas, Lung	0.16 (8/48)	0.19 (9/48)	N.S., results given 6 mo. after injection	N.S.	Gargus et al., 1969
						Ditto, Male	51	9, Adenomas, Lung	0.17 (9/51)	0.23 (12/51)			
Bis(1-chloro-ethyl)ether	0.3mg	10mg/kg	Nujol, 0.05ml	1/wk x 685 days	Left Flank	Mice, ICR Swiss, Female, 8wks, wgt. N.S. (assume 30gr.)	30	4, Sarcomas, Injection Site (20% increase in pulmonary adenomas over non-treated control group)	0.13 (4/30)	0.13 (4/30)	581	669	VanDuuren et al., 1972
Bis(2-chloro-ethyl)ether	1mg	33mg/kg	Nujol, 0.05ml	1/wk x 685 days	Left Flank	Mice, ICR Swiss, Female, 8wks, wgt. N.S. (assume 30gr.)	30	2, Sarcomas, Inj. Site	0.07 (2/30)	0.07 (2/30)	419	658	VanDuuren et al., 1972
Vehicle Control Data	X	X	Peanut oil, 0.5ml	Single Injection	Middorsal Area	Mice, ICR Swiss, Female, 24-72hrs., ~2gr	20	5, Adenomas, Lung	0.25 (5/20)	0.25 (5/20)	N.S.	N.S.	Gargus et al., 1969
						Ditto, Male	30	2, Adenomas, Lung	0.07 (2/30)	0.07 (2/30)	N.S.	N.S.	
"	X	X	Nujol, 0.1ml	1/wk x 313 days	Left Axillary Area	Rats, Sprague-Dawley, Female, 9wks, 120-125gr	20	No Tumors at Injection Site 1, Fibroadenoma, Breast 1, Adenocarcinoma, Breast				486	VanDuuren et al., 1969
	X	X	Nujol, 0.05ml	1/wk x 650 days	Left Flank	Mice, ICR Swiss, Female, 8wks, wgt. N.S. (assume 30gr.)	30	No Tumors				663	VanDuuren et al., 1972

*NAE: not attributable to haloether exposure. Not considered in columns X and N.
N.S.: not specified

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carcinogenicity of this haloether is also indicated in mice receiving only a single injection. However, a different pattern is evident. Although one papilloma and one fibrosarcoma were noted at injection sites, the great majority of tumors appeared as lung adenomas (Gargus _et al_., 1969). In this study, positive carcinogenicity was defined as a mean number of adenomas (column N, Table 40) in the experimental group at least double that of the vehicle control groups. This criteria is adopted from Shimkin and coworkers (1966) and Zweifel (1966). Applying this criteria to the total test group, both males and females, a ratio of $\frac{0.64}{0.14}$ (4.56) clearly indicated a positive response. Most striking, however, is the marked differences in response between males and females. These are summarized below from Table 40.

	X Mean Number of Mice With Tumors	N Mean Number of Tumors per Mouse	Nexp/Ncontrol
Bis(chloromethyl)-ether, Females	0.4	0.46	1.84
Bis(chloromethyl)-ether, Males	0.5	0.82	11.70
Vehicle Control, Females	0.25	0.25	---
Vehicle Control, Males	0.07	0.07	---

Although the incidence of tumor development (X) is not significantly different between males and females, BCME fails to meet the criteria for a positive carcinogen in females but far exceeds the criteria in males.

Similar sex-related differences are seen in the response of mice to a single injection of CMME (Gargus et al., 1969). Here, the ratio of the mean number of tumors in the haloether exposed group to the control group is 1.5 (0.21/0.14) if males and females are considered together. For females, however, the ratio is only 0.72 (0.18/0.25) - a tumor incidence below the control level. Males, on the other hand, have a ratio of 3.3 (0.23/0.07), which meets the criteria for carcinogenicity. Caution is required in the interpretation of these results, however, because the CMME used was contaminated with 0.3-2.6% BCME.

The data presented by Van Duuren and coworkers (1968 and 1972) may indicate a differential response between species. In female rats, repeated injections of CMME produced only marginal activity (Van Duuren et al., 1969). In female mice, however, at a comparable dose per unit body weight, one-third of the animals developed sarcomas at the injection site (Van Duuren et al., 1972). In addition, mean survival time was not significantly decreased in rats but did drop from 643 to 496 days for mice. Although mice received injections for 685 days and rats were treated for only 300 days, the appearance of the first mouse tumor at day 308 seems to indicate that the greater response in mice is not entirely an artifact of the longer treatment period. As noted in Table 40, no tumors appeared in the negative control group of mice (nujol injections) over 643 days (Van Duuren et al., 1972).

Bis(1-chloroethyl)ether produced less than half the number of sarcomas in mice at the injection site as did CMME but was the only haloether tested by Van Duuren and associates (1972) that resulted in an increased incidence of lung adenomas. Bis(2-chloroethyl)ether caused no lung adenomas and only half as many injection site sarcomas as bis(1-chloroethyl)ether. Neither of these ethyl ethers resulted in decreased median survival time in mice (Van Duuren *et al.*, 1972). Thus, by potency, the haloethers tested by subcutaneous injection follow the same order as in dermal application: BCME > CMME > bis(1-chloroethyl)ether > bis(2-chloroethyl)ether.

(iii) Inhalation

Inhalation carcinogenicity testing has been limited to those haloethers which have been most strongly implicated as occupational hazards (i.e., BCME and CMME). Parelleling the results of dermal and subcutaneous applications, the symmetrical ether is by far the more potent.

The initial screening of these compounds was performed by Leong and coworkers (1971) using male mice of a strain A/Heston, known to be sensitive to the induction of pulmonary tumors. In addition to two groups exposed to the haloethers, [BCME, 1 ppm; CMME, 2 ppm] both negative and positive (urethane exposed) controls were adopted. In that the experiment was designed to assess occupational hazard, the mice were exposed for six hours per day over periods indicated in Table 41.

Table 41. Pulmonary Tumors in Male Mice After Inhalation of Bis(chloromethyl)ether, Chloromethyl Methyl Ether, and Urethane (modified from Leong *et al.*, 1971)

Compound	Nominal Concn, mg/Liter	Parts per Million	Exposure Duration, Days	Conc X Duration (Ct), Day-mg/Liter	Incidence of Lung Tumor, X/N*	Av No. of Tumors per Tumor-bearing Animal, T/X*	Av No. of Tumors per Animal per Treatment Group, T/N*	T/N experimental / T/N control
Control	...	...	130	...	20/49† (41%)	2.2	0.87	1
Urethan	0.500	138	130	65.000	46/49† (94%)Δ	57.5	54.20	62.4
Bis(chloromethyl) ether	0.005	1	82	0.410	26/47† (55%)	5.2	2.89	3.3
Chloromethyl methyl ether	0.006	2	101	0.606	25/50 (50%)	3.1	1.53	1.76

*T indicates total number of tumors found in the animals; N equals number of animals examined in each category; and X is number of tumor-bearing animals.

† The balance of the 50 animals were cannibalized.

Δ Chi-square tests for significant differences in incidences of lung tumor between control and treated animals (<0.0005).

As described previously, the criteria for carcinogenicity is a two-fold increase in average number of tumors per animal in the exposed group as compared to the negative control. Using this standard, BCME shows definite carcinogenicity while CMME falls slightly short. Further, the significance of the near doubling-tumor incidence with the CMME is questionable because the sample was contaminated with BCME (0.3-2.6%).

Drew and coworkers (1975) indicate that BCME at 1 ppm may be carcinogenic after much more limited exposures. Of 50 hamsters exposed once to 1 ppm BCME for six hours, one animal developed a malignant nasal tumor. Of 50 rats subjected to three exposures, one rat developed an ulcerating squamous cell carcinoma of the skin. Similar spontaneous tumors are not noted for the negative control groups.

The carcinogenic potency of BCME has also been demonstrated at 0.1 ppm by Laskin and coworkers (1971). In this preliminary report, rats exposed to 0.1 ppm haloether for six hours per day, five days per week, for up to 659 days, developed squamous cell carcinomas of the lung and esthesioneuroepitheliomas of the olfactory epithelium. Recently, these investigators have published more detailed studies on both BCME (Kuschner *et al.*, 1975) and CMME (Laskin *et al.*, 1975) administered to rats - male Sprague-Dawley - and hamsters - male Golden Syrian.

In the BCME study, rats and hamsters were exposed to 0.1 ppm of the haloether for six hours per day, five days per week. Fifty rats and one hundred hamsters received this treatment throughout their lifetime. As indicated previously (see Section III-D-2, Chronic Toxicity, Mammals, p. 116), both groups approached 100% mortality after seventy weeks (350 exposures). Of the one hundred hamsters, only one tumor was noted, an undifferential carcinoma of the lung (Kuschner et al., 1975).

Because of the high mortality in these exposures, groups of rats were exposed to BCME as above for periods of two to twenty weeks (10-100 exposures), observed until death, and then examined for tumors of the lung and nose. The results of these exposures are summarized in Table 42.

In calculating the incidence of cancer from these exposures, corrections were made for animals that died early in the experiment (i.e., before cancer could have developed, thus effectively lowering the number of animals at risk). An analysis of induction time in these exposures indicated that the chance of developing tumors before 210 days was 1%. Consequently, cancer incidence was expressed as number of cancer bearing animals per number of animals surviving beyond 210 days in each exposure group. As illustrated in Figure 22, the respiratory tract cancers are clearly correlated to the number of exposures.

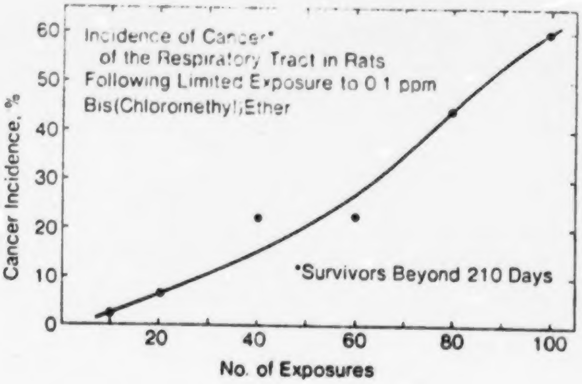

Figure 22. Incidence of Respiratory Tract Cancer in Rats Following Exposures to 0.1 ppm Bis(chloromethyl)ether (Kuschner et al., 1975)

Table 42. Cancer in Rats Following Exposure to 0.1 ppm Bis(chloromethyl)ether for Periods of Two to Twenty Weeks (Kuschner et al., 1975)

	No. of Exposures (No. of Rats)							
Origin and Type of Cancer	100(30)	80(50)	60(20)	40(20)	20(50)	10(50)	Total For All Exposures (200 Rats)	Mean Cancer Time, Days (Range)
Nose								
Esthesioneuroepithelioma	3	9	2	2	1	0	17	447 (266-853)
Malignant olfactory tumor (unclassified)	1	0	0	0	0	0	1	405
Ganglioneuroepithelioma	0	1	0	0	0	0	1	334
Squamous cell carcinoma involving turbinates and gingiva	0	1	0	0	0	0	1	594
Poorly differentiated epithelial tumor	1	1	0	1	1	0	4	462 (253-676)
Adenocarcinoma (nasal cavity)	0	0	0	0	1	1	2	696 (652-739)
Lung								
Squamous cell carcinoma	8	3	2	0	0	0	13	411 (215-578)
Adenocarcinoma	0	0	0	1	0	0	1	877

Leong and coworkers (1975) have examined the inhalation carcinogenicity of BCME at levels of 0.1, 0.01, and 0.001 ppm using rats and mice. The details of these exposures are summarized in Table 37, p. 120. In repeated exposures to 0.1 ppm, 81.6% of the rats developed nasal tumors with some metastasizing to the lungs or lymph nodes. No primary lung tumors were found. Presently completed gross examinations of the rats exposed to the lower levels have thus far revealed no nasal tumors and no increase over controls in the total tumor incidence. Similar results were found with mice. At 0.1 ppm, mice surviving the urinary tract infection showed a significantly ($p<0.005$) increased incidence of lung nodules. This was not found at the two lower levels tested. These results seem to indicate that there is either a very steep concentration response curve or a threshold concentration for BCME inhalation carcinogenicity under these test conditions (Leong *et al.*, 1975).

Laskin and coworkers (1975) conducted similar inhalation exposures to 1.0 ppm CMME. The haloether was not purified and probably contained 1-7% BCME. Male Sprague-Dawley rats and Golden Syrian hamsters were exposed for six hours per day, five days per week, throughout their lifetime (up to 854 days, 565 exposures). Mortality rates in these groups have been discussed previously (see Section III-D-2, Chronic Toxicity, Mammals, p. 116). Of the seventy-four rats exposed, two respiratory tract cancers developed: a squamous cell carcinoma of the lung invading blood vessels and with metastasis to kidney and an esthesioneuroepithelioma of olfactory epithelium. These tumors were found in rats dying at 700 and 790 days, respectively. An undifferentiated pituitary tumor also found in one rat was not attributed to the haloether. Of the ninety hamsters exposed, one hamster killed after 134 days had an adenocarcinoma of the lung and another, which died after 683 days, had developed a squamous papilloma of the trachea.

(iv) Ingestion

Of the haloethers, only bis(2-chloroethyl)ether has been tested for carcinogenicity by oral administration (Innes et al., 1969). However, because this relatively stable compound has been monitored in environmental water samples, the results of Innes and coworkers (1969) are particularly relevant and warrant detailed consideration. In this study, two strains of mice were used and designated strain X (C57BL/6xC3H/Anf,F_1) and strain Y (C57BL/6xAKR,F_1). Seven days after birth, the mice received 100mg/kg/day of bis(2-chloroethyl)ether in water by intubation until the mice were four weeks old. The dose was calculated by the weight of the seven day old mice and not adjusted for weight gain. At age four weeks, the haloether was administered in the food at a concentration of 300mg/kg/day based on the weight and food consumption at four weeks. This schedule was maintained for eighty weeks, using thirty-six mice of each strain evenly divided by sex. The results of this exposure are summarized in Table 43.

As in the subcutaneous administrations previously cited, males of both strains are significantly more susceptible to the tumorigenic effect of the haloether. The only statistically significant increase is in hepatomas of male mice of both strains, with strain X being by far the more sensitive. In this study, hepatomas are classified as liver tumors which have not metastasized. Such a classification does not imply "that these tumors are benign. Indeed, it seems more reasonable to conclude that

Table 43. Tumors in Mice Associated with Oral Administration of Bis(2-chloroethyl)ether (adapted from Innes _et al._, 1969)

	Strain	Number of Mice Necroscopied		Hepatomas		Pulmonary Tumors		Lymphomas		Total Tumors	
		M	F	M	F	M	F	M	F	M	F
Number of Tumors	X	16	18	14	4	0	0	2	0	16	4
	Y	17	18	9	0	2	0	0	1	10	1
Relative Risk Compared to Negative Control	X	--	--	48.79*	Inf.†	0	0	2.34	0	Inf.†*	2.90
	Y	--	--	17.37*	0	1.24	0	0	1.50	6.32†	0.86
Relative Risk Compared to Positive Control	X	--	--	4.259	.331					Inf.†	0.136
	Y	--	--	1.494	0					1.014	0.051

* Increased tumor yield significant at 0.01 level

† Inf. - relative risk calculated as infinite. May result from and may not be significant

the great majority had malignant potential" (Innes et al., 1969). The positive control consisted of combined data from mice exposed to seven known carcinogens: urethane, ethylene imide, amitrol, aramite, dihydrosafrole, isosafrole, and safrole. Although the increased incidence of hepatomas in male mice administered bis(2-chloroethyl)ether compared to the positive control has no absolute definitive value, it is indicative of the highly positive tumorigenic potential of this haloether that has shown only marginal activity in other routes of administration.

b. Biochemical Studies Related to Carcinogenicity

Various attempts have been made to correlate the interactions of haloethers and macromolecules to the carcinogenic activity of these ethers. Van Duuren and coworkers (1972) were unable to demonstrate that BCME, CMME, or α,α-dichloromethyl methyl ether effected isolated salmon sperm DNA, based on changes in absorption, Tm, or buoyant density. More recently, however, the same group of investigators have demonstrated that ^{14}C-labelled BCME is incorporated into the guanine and adenine of isolated calf thymus DNA to a maximum of one millimole of ether per 33 nucleotides (Goldschmidt et al., 1975).

Using epidermal tissue preparation from mice, Slaga and coworkers (1973) have measured the effects of BCME and CMME in the incorporation of tritiated thymidine into DNA, tritiated cytidine into RNA, and tritiated leucine into protein. Paralleling the finding by these investigators that CMME is not an active initiating agent in dermal application to mice (see Table 39), CMME did not induce incorporation patterns differing significantly from control values. BCME, as illustrated in Figure 23, did cause marked variations in all three incorporation patterns.

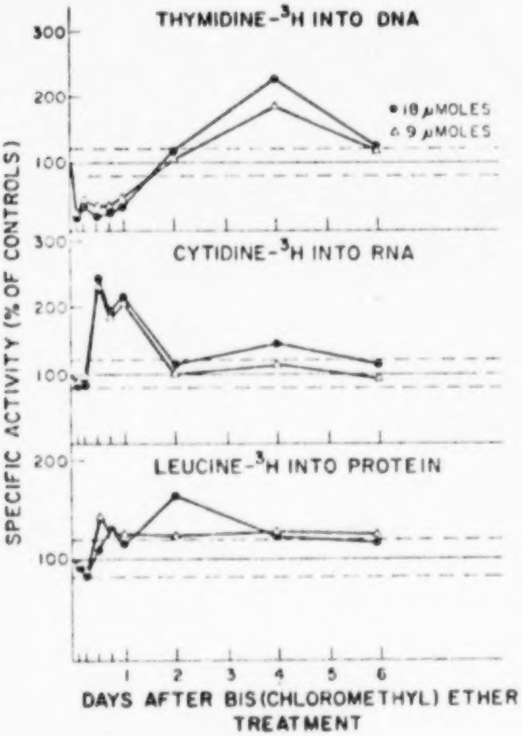

Figure 23. The Effect of Bis(chloromethyl)ether on Various Incorporation Patterns in Mouse Skin Preparations (Slaga _et_ _al_., 1973)

These biochemical effects, however, may not relate solely to the carcinogenic activity of BCME. The initial decrease in thymidine incorporation into DNA, for instance, may in part be due to cell death, higher DNA turnover, or an adverse effect on enzymes involved in thymidine incorporation. Nevertheless, these results are consistent with the high tumor inducing potential of BCME relative to its monochloro analogue (Slaga et al., 1973).

7. Behavioral Effects - No studies encountered.

8. Possible Synergisms - No studies encountered.

E. Toxicity - Invertebrates

Little is known concerning the effect of the chloroethers in invertebrates. Takizawa and Fujita (1974) report that a mixture of 25-90 parts bis(2-chloroisopropyl)ether and 100 parts 0,0-diethyl-0-(2-isopropyl-4-methyl-6-pyrimidinyl) phosphorothioate is effective in controlling Scarabaeidae larvae in soil. The dose is not specified, but the chloroethers are synergistic with the phosphorothioic acid.

Bis(2-chloroethyl)ether appears to have nematocidal properties. A preparation of this ether, 1,3-dichloropropene, and 1,2-dichloropropane (50:30:20) microencapsulated in a vapor permeable gelatin and applied to soil at a concentration of 30-50 ml/m^2 was effective against nematodes for over two weeks (Siebel, 1972). However, bis(2-chloroethyl)ether used alone - concentration unspecified - seemed to have only a slight effect in protecting sugar beets from nematode attack (Saly et al., 1962).

F. Phytotoxicity

Only two reports concerning the effects of haloethers in plants have been encountered. Matsumoto and coworkers (1974) report that bis(2-chloroisopropyl)ether, at an unspecified concentration, promotes root growth in tomatoes. Bis(2-chloroethyl)ether, on the other hand, is highly toxic to sugar beets at concentrations over 150 ml/m^2 (Saly *et al.*, 1962).

G. Toxicity - Microorganisms

Mukai and Hawryluk (1973) have found that BCME and CMME are mutagenic to *Escherichia coli* and *Salomonella typhimurium*. Both chemicals produce dose related increases in mutations in these species. Similar to their carcinogenic potencies, BCME induces mutations at μg levels while CMME produces the same effects at 10 to 100 fold higher levels (Mukai, 1975).

A solution containing bis(2-chloroisopropyl)ether and sodium pentachlorophenol has been reported to be effective in protecting the Japanese cedar, *Cryptomeria japonica*, from the fungus, *Poria vaporaria* (Ishii *et al.*, 1974). However, because the relative quantities of each of the two chemicals are not given, and because pentachlorphenol is itself a potent fungicide (Howard and Durkin, 1973), the actual fungicidal properties of the β-chloroethers cannot be assessed.

IV. Regulations and Standards

A. Current Regulations

Of the haloethers under review, only BCME and CMME are currently under regulation. In 1973, both of these α-chloroethers were cited along with twelve other chemicals as carcinogens and emergency temporary standards were established for limiting occupational exposure (OSHA, 1973). These initial standards limited the use, storage, or handling of the ethers to "controlled areas" in which elaborate precautions were specified to minimize worker exposure. In addition, decontamination, waste disposal, monitoring, and medical surveillance programs were required. These regulations applied to all preparations containing 1% or more of the haloethers. Recently, more detailed regulations have been established for both BCME (OSHA, 1974a) and CMME (OSHA, 1974b). While similar in scope to the emergency temporary standards, these more recent regulations apply to all substances containing 0.1% of the haloethers by volume or weight.

B. Concensus and Similar Standards

The American Conference of Governmental and Industrial Hygienists (ACGIH, 1974) have established TLV's for BCME and bis(chloroethyl)ether.

The TLV for BCME is 1 ppb (about 5 $\mu g/m^3$). This value is based on the known carcinogenic activity of this α-chloroether as discussed previously.

The TLV for bis(chloroethyl)ether has recently been changed from 15 ppm (about 90 mg/m^3) to 5 ppm (about 30 mg/m^3). This value is based on the irritant properties of the β-chloroether to the eye and respiratory tract without reference to its potential oral carcinogenicity.

V. Summary and Conclusions

The chloroethers appear to be the most important commercial haloethers. In terms of environmental hazard, the chloroethers can be divided into two categories, (1) α-chloroethers and (2) the non-α-chloroethers, because of the drastic difference between these two categories in terms of uses, stability, environmental contamination, and toxicity.

Of the α-chloroethers, bis(chloromethyl)ether (BCME) and chloromethyl methyl ether (CMME) have received the most attention. CMME, containing a minor amount (1-7%) of BCME, is used as a chemical intermediate in the production of strong base anion exchange resins. The quantities used have not been reported. BCME can also be formed whenever formaldehyde and a chloride source are present under acidic conditions. The ion exchange resins find applications in deionizing water and as a method of separation in many industrial chemical processes (e.g., recovering uranium from sulfuric acid leach liquors). The compounds are unstable in water ($t_{\frac{1}{2}} = <1$ sec and <1 min for CMME and BCME, respectively), although they may be stable for relatively long periods of time in the vapor phase ($t_{\frac{1}{2}} > 390$ minutes and >25 hrs for CMME and BCME, respectively). Under both aqueous and vapor phase conditions, BCME is more stable.

Past contamination of the working environment in the ion exchange manufacturing plants has been well documented. Presently, elaborate precautions are taken to prevent exposure to workers and precautions appear to be taken to prevent contamination of the external environment. However, the latter has not been well documented. Inadvertent BCME contamination from contact between formaldehyde and hydrochloric acid has been considered and research is continuing in the textile and paper industries and medical research field. Monitoring in a medical research laboratory resulted in no detection of BCME. However, low concentrations (< 2 ppb) of BCME have been detected in some textile plants. Contamination of the external environment from this source may prove to be insignificant. On the other hand, sizable concentrations (210-1500 ppb) have been noted above formalin slurries of Friedel-Crafts chloride salts (chloromethylating agent). No extensive monitoring of the air or water effluent from the ion exchange plants or industries that possibly produce BCME inadvertently has been reported. Detection of chloromethyl ethyl ether and chloromethyl ether in the drinking water of the New Orleans area has been reported, but the studies are probably in error considering the high rate of hydrolysis of α-haloethers.

The potential hazard posed by these α-chloroethers has been convincingly demonstrated. At high levels, both BCME and CMME are extremely corrosive to living tissue because of their chemical reactivity. Of greater concern, however, is the inhalation carcinogenicity of these compounds in the low ppm range. BCME is clearly the more potent. In six hour exposures to 0.1 ppm, this chloroether has been shown to induce respiratory tract cancer in rats directly related to the number of exposures. In rather extensive epidemiological investigations, the incidence of respiratory tract cancer in men exposed to BCME has been shown to be positively related to both the intensity and duration of exposure. The carcinogenicity of pure CMME has not been demonstrated because of BCME contamination of the CMME used in the tests. Commercial grade CMME (containing 1-7% BCME) at 1 ppm has been shown to induce respiratory cancers in rats after multiple six hour exposures. Occupational exposure to CMME with concomitant

BCME exposure has been associated with increased respiratory tract cancers in man. Thus, exposure to either of these α-chloroethers may be regarded as carcinogenic.

In summary, the α-chloroethers appear to be, for the most part, occupational hazards since they are carcinogenic, but seem to be unstable in the environment. However, because they are extremely carcinogenic, some selective monitoring is probably needed to insure that sizable quantities of these compounds, especially BCME, are not reaching the external environment. Because these compounds are relatively stable in the vapor phase, sources of atmospheric contamination are particularly important to consider. Also, the researchers that have reported detection of α-chloroethers in the New Orleans area drinking water should be contacted to determine the validity of their results.

In contrast to the α-chloroethers, the β-chloroethers are widespread environmental contaminants. There are three β-chloroethers that are used in reasonably large commercial quantities: bis(2-chloroethyl)ether, bis(2-chloroisopropyl)ether, and bis(2-chloroethoxy)methane. The last compound is an acetal, not an ether, but was considered because of its close chemical similarity.

Bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether have been used as dewaxing agents for lubricating oils, solvents and penetrants in the textile industry, and as chemical intermediates. Bis(2-chloroethoxy)methane is the principal monomer in the production of polysulfides. The quantities of these materials that are presently produced and used are unreported. Sizable quantities of bis(2-chloroethyl)ether were produced (26 million lbs in 1960) and sold (15 million lbs in 1960) when the chemical was a cheap by-product in the chlorohydrin synthesis of ethylene oxide. Since 1972, no ethylene oxide has been synthesized by the chlorohydrin route. However, 70% of the propylene oxide produced is manufactured using the chlorohydrin route (1973 capacity - 1,227 million lbs).

Bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether are both more stable to chemical hydrolysis than the α-chloroethers ($t_{\frac{1}{2}}$ = 12.8 days for bis(2-chloroethyl)ether in a water-dioxane solution compared to 18 minutes for CMME. The preliminary studies on biodegradability reported in the literature are difficult to interpret, but monitoring data in the Ohio River would suggest that bis(2-chloroisopropyl)ether does not degrade rapidly. Acetals, such as bis(2-chloroethoxy)methane, are much less stable to chemical hydrolysis, especially under acid conditions.

Contamination of raw and drinking water by bis(2-chloroethyl)ether and bis(2-chloroisopropyl)ether is well documented by monitoring. In fact, bis(2-chloroethyl)ether was noted as a water contaminant as early as 1963. These compounds have been detected in the Kanawha, Mississippi, Ohio, and Delaware Rivers. One study showed that a glycol plant having a propylene oxide plant capacity of 130 million lbs/year had a daily effluent of approximately 150 lbs. If similar losses take place from other propylene oxide chlorohydrin plants, the quantity released in 1973 would be approximately

600,000 lbs of bis(2-chloroisopropyl)ether. This same study showed that conventional drinking water treatment processes only removed 60% of the bis(2-chloroisopropyl)ether. On the other hand, Dow Chemical, a major producer of propylene chlorohydrin, states that they burn all their by-product bis(2-chloroisopropyl)ether, although they do emit 20 lbs/day of the ether in their air effluent. Since ethylene oxide is no longer being made from ethylene chlorohydrin, bis(2-chloroethyl)ether contamination must be a product of some other source. Recently, bis(2-chloroethyl)ether has been detected in the effluent from a Rohm and Haas plant in Philadelphia. The compound was being used as a chemical intermediate in the production of detergents. Bis(2-chloroethyoxy)methane has been reported in the treated effluent from a synthetic rubber plant but has not been detected in raw or drinking water.

The well-documented chloroether contamination resulting from the propylene chlorohydrin process suggests that other chlorohydrin processes might be sources of chloroether contamination. The chlorohydrin synthesis of epichlorohydrin from alkyl chloride is such a process (capacity in 1975 - 495 million lbs). Bis(2,2'-dichloroisopropyl)ether would be the major ether formed, and it should be stable to chemical hydrolysis since it is not an α-chloroether. No environmental detection of this compound has been reported.

The potential dangers of such widespread exposure to the β-chloroethers is difficult to assess. Unlike the α-chloroethers, these compounds are not extremely corrosive. Available information from standard toxicity tests indicates that these compounds have little effect at concentrations below 100 ppm. Bis(2-chloroethyl)ether is a respiratory irritant and can be fatal if inhaled at concentrations above 100 ppm. Bis(2-chloroisopropyl) ether is fatal at slightly greater concentrations (~ 300 ppm) and may cause liver as well as lung damage. By far, the greatest concern, however, is the apparent oral carcinogenicity of bis(2-chloroethyl)ether. This compound has been shown to induce hepatomas in young mice at concentrations of 100mg/kg/day x 7 days (incubation) followed by 300mg/kg/day x 21 days (in diet). By all other routes of administration - inhalation, dermal, subcutaneous - this and other β-chloroethers show no marked carcinogenic activity.

The findings of this single study raise serious questions about the potential danger of β-chloroether contamination in fresh water. If bis(2-chloroethyl)ether is an oral carcinogen, then bis(2-chloroisopropyl)ether is also suspected. Further tests on both of these compounds are clearly indicated to determine not only a dose-response effect, but also the proximal carcinogen(s). Bis(2-chloroisopropyl)ether is currently being evaluated for carcinogenicity by the National Cancer Institute (1975). The results of this investigation should be carefully reviewed. If the oral route is not employed, oral carcinogenicity tests should be begun as soon as possible.

Information on the sources of these two compounds needs to be more exact than is presently available. It appears that the chlorohydrin synthesis of propylene chlorohydrin is the major source of bis(2-chloroisopropyl)ether. However, much better effluent and ambient monitoring data is necessary. Information on the quantities of the ethers that are produced and a more detailed breakdown of their uses is required. Better information on the biodegradability of these compounds is also needed. The possibility of contamination from epichlorohydrin production should also be considered.

Thus, since the β-chloroethers are (1) produced or may be formed as by-products in large quantities, (2) are released to and appear to persist in the environment, (3) can pass through drinking water treatment plants, and (4) may be carcinogenic, it is suggested that intensive research and study of these compounds be undertaken.

The potent carcinogenicity of the α-chloroethers, particularly BCME, requires that effort be continued to understand the parameters involved in their information and that efforts be undertaken to assure that these materials are not released to the environment.

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